MYASTHENIA GRAVIS

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Preface

Although the clinical picture of myasthenia gravis was basically recorded in the late nineteenth century, there was little the clinician could do for the patient until twenty-odd years ago. Since then, and particularly in the last five years, new drugs and techniques of management have given the physician tools with which to make the myasthenic patient lead a more normal life The numerous papers published in recent years on therapy, management and basic factors in this syndrome now make it an appropriate time to sum up our present knowledge The problems of diagnosis, selection of drugs, the employment of the Tensilon test, not only for diagnosis but also as a guide to management, have to be solved daily for an ever increasing number of patients It has been my privilege, as organizer and Physician-In-Charge of the Myasthenia Gravis Clinic at The Mount Sinai Hospital in New York City, to see and treat over 350 patients with this disorder The Clinic, located in so large a city where most of the patients reside, has permitted continuous follow-up, so that the patient is seen not only in the acute form which requires hospitalization, but also in his daily work-a-day world This has been a most gratifying experience and can be for any physician caring for these individuals

I receive numerous requests from physicians to clarify the daily problems associated in the care of the myasthenic patient, both as a physician and as former Secretary and now Vice-Chairman of the Medical Advisory Board of The Myasthenia Gravis Foundation, Inc When it was suggested that I write a monograph on the subject, I felt that there was a real need, inasmuch as the only previous one, published by Goñi of South America in 1946, is now out of print

The emphasis in this book has been placed on practical considerations in diagnosis, treatment and management Individual case histories are cited in various chapters to clarify the test Current knowledge in the basic sciences affecting myasthenia gravis has been included in the chapter on Pathology written by Dr Harvey Mendelow, and in the chapter on Physiology which my colleagues Drs David Grob, William L Nastuk, Francis F Foldes and Daniel Feldman read and improved by valuable suggestions It is hoped that this book will also satisfy the needs of medical students who desire access to more information on this subject than that available in the usual textbooks of medicine and neurology. In general, proprietary names of drugs most familiar to the clinician have been used, the generic term being given the first time a drug is mentioned

I have received help, advice and encouragement from many sources during the years I have been studying myasthenia gravis I would like to thank my patients who have given their whole hearted cooperation and

confidence in my endeavors To my present and former clinical associates, too, who have cooperated in the various "Studies in Myasthenia Gravis," my sincere thanks I am indebted to Dr. Lawrence I. Kaplan, who has been associated with me since the founding of the Clinic and who read and helped in the writing of the chapters on Diagnosis and Differential Diagnosis. Most of all I would like to express my sincere gratitude to Dr. Alexander B. Gutman, my chief, who made all this work possible through his extensive cooperation and constructive suggestions through the years To all the residents and interns who have lost many a night's sleep in caring for the patient in crisis, thanks. A special acknowledgment goes to Dr. Thomas C. Fleming for his sincere cooperation and advice.

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Contents

Dedicated To
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CHAPTER I

History

Myasthenia gravis is a disorder characterized by fatigability and abnormally rapid exhaustion, with loss of strength in the muscles under voluntary control and a return of strength, at least in part, after a period of rest.

The term myasthenia gravis comes from the Greek *mys* (muscle), *asthenia* (weakness), and from the Latin *gravis* (heavy) and implies a marked or severe muscle weakness. This weakness does not necessarily have to be "gravis" to be "myasthenia" Undoubtedly, because of the mild character of the symptomatology in some cases, many remain undiagnosed and untreated

Jolly,[1] in 1895, was the first to use the name "myasthenia gravis pseudoparalytica" to describe this syndrome in two boys, aged 15 and 14 years respectively. In the first patient, a number of symptoms had been present for eight months. When his muscles were stimulated repeatedly with faradic current, a reaction of asthenia was promptly demonstrated by recorded tracings. This is the "myasthenic reaction," or Jolly test The boy died suddenly while eating, and at autopsy no abnormal findings were observed either in the nervous system or in the muscles.

Jolly's second case had symptoms for over a year, beginning with ptosis Subsequently, the illness progressed to involve speech, chewing, holding the head erect, and, finally, marked weakness in other muscle groups The child was always better after rest, particularly on arising Jolly suggested physostigmine as a form of treatment, but apparently never tried it.

In 1903, Guthrie[2] reported the work of an earlier English colleague, Thomas Willis,[3,4] who in 1672 recognized the chief symptoms of asthenia of voluntary muscle with recovery after rest. Willis' book, *De Anima Brutorum*, written in Latin and giving illustrative cases, was translated into English by S Pordage in 1683.

"Nevertheless, those labouring with a want of Spirits, who will exercise local motions, as well as they can, in the morning are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of the Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot. At this time I have under my charge a prudent and an honest Woman, who for many years hath been obnoxious to this sort of spurious Palsie, not only in her

Members, but also in her tongue; she for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes as mute as a Fish, nor can she recover the use of her voice under an hour or two."

It was over two hundred years before this syndrome was again referred to in the medical literature. In 1877, Samuel Wilks,[5] an English physician at Guy's Hospital, London, reported a case with symptoms suggestive of myasthenia gravis. Autopsy revealed a medulla oblongata "quite healthy to the naked eye, and the microscope discovered no manifest change in the tissue."

Erb,[6] in 1879, was the first physician to give a reasonably full account of the syndrome in three patients. It is interesting to note that his patient, a man of 55 years who was first seen in 1868, is the first recor case to show remission. Because he was treated with electricity—galv ism—for six months, Erb believed that this was the cause of his improv ment. The second patient, a woman 30 years of age, showed freque fluctuation in the severity of the disorder. At one time she was nearl normal, later, her speech became nasal and there was marked generalized weakness. After a period of remission she died suddenly during her sleep. Erb's paper is important for clearly defining the chief symptoms of myasthenia gravis, particularly the bulbar involvement, the progress of remissions and exacerbations, the sudden death, and the frequency of pto as the initial complaint. However, he gave no name to the syndrome.

Eisenlohr,[7] in 1877, added another case report and is chiefly notable fo his observation of the variations in the patient's symptoms in the course of a single day. Oppenheim,[8] in 1887, in his report of a case, was chiefly concerned with the differential diagnosis between myasthenia gravis and hysteria.

Shaw,[9] in 1890, re-emphasized Willis' observation that the patient's "symptoms were but slight in the morning, but became more evident as the day advanced." Shaw also called attention to the "copious secretion of frothy mucus" and gives a vivid account of terminal respiratory arrest, with failure of artificial respiration. Bernhardt,[10] in 1890, reported the striking changes in myasthenia gravis seen in the extraocular movements. His case showed a three-year remission after the disorder had been present for ten years.

Herman Hoppe,[11] in 1892, working in Oppenheim's clinic in Berlin, was the first American physician to report a fully studied case, a case which he compared in detail to those of Wilks, Oppenheim and Eisenlohr. His s the first comprehensive review of the syndrome. Further cases were reported by Remak[12] in 1892, Dreschfeld[13] in 1893, and Goldflam[14] in 1893. he latter added greatly to knowledge of the disorder, and his name cou-

pled with Erb's as the Erb-Goldflam symptom complex is even currently

gravis is primarily a disease of the motor system, with only occasional pain or paresthesias, chewing, swallowing and eye movements are most affected at first, followed by involvement of the trunk and extremities The disease rarely has its onset in the arms or legs The muscular involvement is usually symmetric The muscles supplied by the facial nerve are always involved, particularly the middle and lower branches, the muscles of mastication and those of the neck are the next most commonly affected Stimulation results in rapid weakness Most patients are worse in the afternoon Twenty or thirty movements often bring the muscle response to zero Daily remissions and relapses occur, but remissions may last as long as four years The knee jerk may be exhausted by stimulation. Death may occur very suddenly. Most of Goldflam's observations are valid today, in fact, little has been added to the clinical description of myasthenia since his time. Viets[15] has said that Goldflam's paper in many ways is the most important ever written in the history of the condition.

Soon after Goldflam's and Jolly's reports, papers appeared from many sections of Europe and America In 1897, Cohn[16] reported a case of myasthenia gravis and fixed the name given to the syndrome by Jolly. In the same year, Collins[17] first pointed out that myasthenic symptoms were increased at the menstrual period In 1898, Mailhouse[18] reported myasthenia in a boy aged two years and nine months In America, two cases were reported at the 25th Annual Meeting of the American Neurological Association[19] By the year 1900, the syndrome had become widely recognized

Campbell and Bramwell[20] reviewed the entire literature to 1900, abstracted each case and compiled a table giving the major symptoms and signs Of interest is the fact that in 1900 DeBuck[21] described a case in which some muscle atrophy occurred This caused him to be disturbed about the accuracy of the diagnosis DeBuck reported a second case with Broeckaert[22] and reviewed the literature. They considered their case to be the ninety-first.

Because there was no clear-cut test, the diagnosis of myasthenia gravis had to be made clinically after excluding other neurologic lesions. In 1901, the first case of a thymoma in a myasthenic was reported by Laquer and Weigert.[23] Subsequently, many reports of involvement of the thymus were recorded.

The early part of the 20th century continued in the same vein as the close of the 19th century, with recording of clinical and autopsy findings

in this syndrome. Soon the attention of the physiologist became centered on the nature of the asthenia Elliot,[24] in 1904, suggested that a chemical substance might be liberated from nerve endings, but no direct experimental evidence was offered. The work of Loewi,[25,26] reported in the Harvey lecture of 1932, upon the transmission of cardiac effects being due to acetylcholine was a major advance for which he received the Nobel prize. Dale,[27-29] in 1936, showed that acetylcholine is liberated from the terminals of motor nerves and serves as a transmittor of impulses to the muscle fibers Electromyographic techniques[30,31] were applied to the problem and aided in elucidating the mechanism of the block at the neuromuscular junction. In England, A Wilson and Stoner[32] studied this problem, while in this country Feldberg,[33] Nachmansohn,[34] Grob,[35] Harvey,[36-39] Nastuk,[40] etc., studied the physiology and pharmacology of the myasthenic problem

In 1930, Dr. Harriet Edgeworth,[41,42] who was herself a myasthenic took

he ephed-

, still used

as an adjunct in therapy.

In 1934, a patient with muscle weakness was admitted to St. Alfege's Hospital, London. Mary Walker was the resident physician She presented the case to the Attending Physician, who made the diagnosis of myasthenia gravis. But it was Dr. Walker who gave the patient an injection of eserine. And thus the modern era of therapy of myasthenia gravis was started in 1934 with her report in *Lancet*.[43,44]

Because eserine (physostigmine) had so many side-reactions, a search was in progress for a number of years for an analogue Aeschlimann[45] in Switzerland synthesized Prostigmin, which was soon being tried for myasthenia gravis. In America, Viets used Prostigmin, and with his resident, Schwab, published a basic paper[46] in which Prostigmin was used for the diagnosis of myasthenia gravis This test has withstood time and is still being widely used In 1935, Viets organized the first clinic for the treatment of myasthenia at the Massachusetts General Hospital In 1937, Kennedy and Moersch[47] published a comprehensive report of their cases.

In 1939, Blalock[48] and associates described an instance of apparent success in the treatment of myasthenia gravis with removal of a thymic tumor in a myasthenic patient The paper was most timely and is generally credited with introducing the era of thymectomy. Keynes[49] in England became a staunch advocate of this procedure Large series have been reported by Eaton and Clagett[50] of the Mayo Clinic and the Massachusetts General group[51] Andrew Wilson[52] has studied the effects of thymic gland extracts

With the close of World War II, it was found that the Germans had

perfected a nerve gas which worked by poisoning the cholinesterase enzyme In the late 1940's and early 1950's we find four of these compounds, diisopropyl fluorophosphate (DFP),[53] hexaethyltetraphosphate (HETP),[54] tetraethylpyrophosphate (TEPP),[55] and octamethyl pyrophosphoramide (OMPA),[56-58] being tried in the treatment of myasthenia gravis Because the range between toxic and therapeutic actions was so narrow, their use was gradually discontinued

The endocrines, especially the adrenocorticotropic hormones, were given therapeutic trials without much success in the late 1940's and early 1950's[59-64]

In 1952, a rapid diagnostic test (results within two minutes) was reported from The Mount Sinai Hospital, New York City, by Osserman and Kaplan with the use of Tensilon (edrophonium) chloride[65-68] Further experience with the test showed it to be valuable in differential diagnosis and a useful adjunct in the evaluation and stabilization of treatment requirements in the patient with myasthenia gravis[66] The use of the Tensilon test made it evident that weakness could be induced with overdosage of anticholinesterase drugs, and the need to avoid cholinergic (overdosage) reactions became apparent.[67]

In 1954 and 1955, two new drugs for the treatment of this syndrome were introduced into the therapeutic armamentarium Mestinon bromide was first reported in this country from The Mount Sinai Clinic in New York City by Osserman et al[69,70] and has been widely accepted Mytelase, first reported by Schwab[71,72] from Massachusetts General Hospital, Boston, Massachusetts, is fast proving its worth. It has also been reported by Westerberg[73] Currently, three drugs, Prostigmin, Mestinon and Mytelase are available for treatment.

In 1955, Wilson working in Nachmansohn's laboratory synthesized chemical, para-amino aldoxime (PAM) which reversed the action of nerv gas poisons[74] In 1957, Grob reported that this chemical could rever the cholinergic effects of quarternary ammonium salts[75]

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CHAPTER II

Pathology

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THE NERVOUS SYSTEM IN MYASTHENIA GRAVIS

BECAUSE OF THE close resemblance between some of the symptoms of myasthenia gravis and those of bulbar palsy, it is understandable that the earliest pathologic investigations in myasthenia gravis were focused on the central nervous system. The majority of these studies produced completely negative results, but the situation became somewhat confused as a result of scattered case reports claiming a wide variety of pathologic lesions in different areas of the brain stem, midbrain, etc. Emphasis was placed on focal ganglion cell degeneration and neuronophagia in thalamus and brain stem, perivascular lymphocytic infiltration and hemorrhage. McKendree and Wolf [1] described calcium and iron pigment deposition in the globus pallidus.

In a review of these cases, Westphal and Meyer [2] pointed out that too much stress is placed on minor ganglion cell changes in the brain stem in myasthenia gravis since these are seen in the normal as well as in a wide variety of other diseases. The same is true for the perivascular lymphocytic collections and hemorrhages. These are real lesions but their sparsity and distribution make their significance rather doubtful. Their location in the brain fails to demonstrate any correspondence between the distribution of the symptoms actually present and those which might be expected to occur as a result of the particular nerve tracts and nuclei involved. To be considered also is the possibility that these central nervous system lesions are secondary to dyspnea and faulty oxygenation of the brain.

McKendree and Wolf (1935)[1] reported a case of "myasthenic syndrome" in a young girl following a presumed episode of postinfluenzal encephalitis and described the pathologic findings in the brain. In attempting to establish some relationship between myasthenia gravis and encephalitis, they concluded that well-documented cases of myasthenia gravis gave only equivocal or negative histories for previous encephalitis, while, in contrast, the "myasthenic syndrome" following some well-defined cases of epidemic encephalitis was not clear-cut and lacked several features of the

classical clinical syndrome of myasthenia gravis Eighteen necropsies in 25 fatal cases of myasthenia gravis and/or thymoma at The Mount Sinai Hospital in New York City revealed no significant abnormalities on gross and microscopic examination of the brain. The spinal cord and peripheral nerves were also examined in several cases, with similarly negative results The recent postmortem study of Rowland et al[3] gives further confirmation of the prevailing conclusion that no characteristic pathologic changes are found in the central nervous system or peripheral nerves in myasthenia gravis.

The Striated Muscle in Myasthenia Gravis

Since the studies of Jolly in 1895, students of myasthenia gravis have been puzzled by the lack of correlation between the prominent weakness and abnormal physiologic responses of certain voluntary muscles and any demonstrable pathology in the involved muscles In a small percentage of cases atrophy of the affected muscles may be present, sometimes of a severe degree, but usually no gross changes are observed

There are certain histologic changes of the striated muscle in this disease which are usually characteristic when present The first of these is the so-called "lymphorrhage" This consists of a focal collection of small mononuclear cells and lymphocytes often found in a perivascular position in the striated muscle The lymphorrhage was first noted by Weigert (1901)[4] He interpreted the lesion as metastatic tumor but this was soon disproved Buzzard (1905)[5] described the lymphorrhage in some detail in a postmortem study of five cases of myasthenia gravis and considered it a pathognomonic finding It is now known that the lymphorrhage can be found in over 50 per cent of myasthenics It may be present with even greater frequency depending on how extensively the striated muscle is sampled at postmortem examination or by biopsy in the living patient. The numbers and locations of lymphorrhages usually cannot be related to the clinical course of the disease and the muscle groups most prominently affected may be completely free of these lesions. Because of this [illegible] phor- [illegible] The [illegible] s of exophthalmic goiter,[6] rheumatoid arthritis, etc

As more case reports and postmortem studies accumulated, it became evident that the lymphorrhage was not the only evidence of striated muscle pathology in myasthenia gravis Many investigators[3,5,7,17] described individual examples covering a whole spectrum of changes in the voluntary muscle, ranging from the lymphorrhage to the severest focal and diffuse muscle necrosis accompanied by an acute and chronic inflamma-

tory reaction Russell,[15] in 1953, finally classified these striated muscle lesions in a comprehensive postmortem study of eight cases of myasthenia gravis, in four of which thymomas were also present. She described three classes or groups of muscle change. Type I consists of an acute coagulative necrosis of the muscle fiber. This begins with eosinophilic swelling and loss of cross striations and development of a "fibrinoid" cytoplasm staining deep purple with phosphotungstic acid hematoxylin. A cellular inflammatory exudate composed of macrophages, lymphocytes, plasma cells and even polymorphonuclear leucocytes accompanies this alteration Eventually the necrosis progresses to fragmentation of the fiber within the sarcolemmal sheath and removal by phagocytes. Abortive attempts at regeneration give rise to the characteristic multinucleate muscle "giant" cells scattered throughout the lesion. The necrosis may be limited to one fiber in a highly selective fashion or may be extensive enough to be seen in low-power microscopic or even gross examination of the affected muscle Type I change was seen in six of Russell's eight cases in varying locations and degrees.

Type II concerns the lymphorrhage. This is thought to begin as a solitary muscle fiber atrophy with basophilic cytoplasm and loss of cross striation The sarcolemmal nuclei increase in number and take a central position in the fiber. A focal lymphocyte and mononuclear cell collection accumulates Eventually the affected fiber disappears, leaving behind the lymphorrhage Type II lesion was seen in all of the eight cases examined. Type III consists of simple focal muscle changes with eosinophilia and swelling, but no loss of striation and no inflammatory reaction It was encountered in seven of the eight cases This was considered a nonspecific change in contrast to types I and II.

These three types of lesions may occur singly or in any combination in a given striated muscle Striking degeneration was noted specifically in this series in the striated muscles of the tongue, palate, pharynx and upper esophagus in those cases clinically showing the bulbar type of paralysis. Russell[15] pointed out the well-known immunity of smooth muscle to this reaction even when adjacent to prominent striated muscle lesions, for example, in the upper esophagus

Other postmortem series confirm the impression that striated muscle pathology is a frequent finding in myasthenia gravis. In 26 necropsies Rowland et al.[3] found lymphorrhages present in 16, muscle fiber alterations in 12 cases and frank necrosis with reactive myositis in 3 cases. Ringertz[13] noted lymphorrhages in 7 of his 11 cases. Even in a series of individual muscle biopsies in living patients with myasthenia gravis, Stortebecker[16] was able to find focal myositis in 6 of 13 patients. In The Mount Sinai Hospital series, frank myositis of the type I variety has been encountered



Fig 1 Striated muscle in myasthenia gravis Minimal focal necrosis with inflammatory cell reaction ("lymphorrhage") x 280

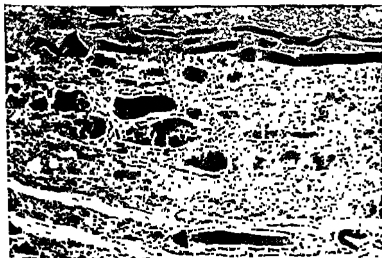


Fig 2 Striated muscle in myasthenia gravis with thymoma Extensive diffuse necrosis with severe reactive myositis Note the fragmentation of muscle fibers within the sarcolemmal sheath x 133

in 9 of 25 cases (36 per cent). Eight of these nine examples were associated with a coexistent thymona. Lymphorrhages were noted in five additional cases.

It is now generally agreed that striated muscle lesions are a part of the pathology of myasthenia gravis. Their pathogenesis and significance in the clinical picture remain unsolved. Buzzard[5] proposed the theory of a toxin as a cause of myasthenia gravis, but the relationship to the thymus and the striated muscle lesions was never well explained. Querido[18] thought that myasthenia gravis represented a generalized vascular disorder with muscle pathology as part of a chronic proliferative perivasculitis. During the height of enthusiasm for the "focus of infection" theories regarding the cause of many obscure diseases, Butt[10] claimed to have demonstrated Gram-positive cocci in the muscles of five of seven patients with myasthenia and supported the toxin concept of Buzzard. This idea has recently been revived by Stortebecker[16,19] who found evidence of high antistreptolysin, antistaphlolysin and E. coli agglutination titers in the sera of patients with myasthenia gravis having muscle changes on biopsy, as well as pathogens on throat culture. Other studies, including our own, fail to confirm the presence of bacteria in the muscle lesions.[12,20] Intensive antibiotic therapy of a selected series of myasthenics failed to improve their clinical status.[21] Giordano and Haymond[11] point out the resemblance of the extensive muscle destruction in their cases to the changes seen in dermatomyositis and scleroderma and question the possibility of some kinship to the "collagen diseases."

That these striated muscle lesions are not specific for myasthenia gravis is proven by their presence in hyperthyroidism, Addison's disease, rheumatoid arthritis and even in 14 per cent of 419 nonrheumatic cases at necropsy.[22] Russell[15] and others conclude that these changes are not specific but are related to the striated muscle weakness and to the interference with physiologic function in all these diseases. In myasthenia gravis, in which the abnormality of the muscle is supposedly spontaneously reversible during remission or as a consequence of drug therapy of various types, these pathologic changes may well represent a "point of no return," i.e., the muscle defect has been so prolonged or severe as to result in necrosis or atrophy of the affected fibers. Keynes[23,24] has emphasized this possibility in his discussion of post-thymectomy remissions in which residual muscle deficit remained.

Detailed studies of the intramuscular nerve-endings by Adams et al[25] and Woolf et al,[26] have failed to reveal any changes in morphology which might be specifically related to this disease. The only alterations seen with the most delicate histologic techniques, including supravital staining before biopsy, were associated with degeneration of muscle fibers and

were thought to be secondary to loss of contact of the intramuscular nerve-endings with the degenerated fibers Similar alterations are found in completely different conditions, such as dystrophia myotonica Histochemical techniques such as the identification of the sites of cholinesterase activity by the method of Koelle[21] applied to this problem have been similarly unrewarding[28] No difference in cholinesterase content of normal and myasthenic muscles has been found at necropsy or by biopsy techniques Further refinements in histochemical techniques seem most promising and may eventually prove to be the means of demonstrating the nature of this neuromuscular junction defect.

The Heart in Myasthenia Gravis

Most studies in myasthenia gravis performed prior to the last twenty years are uniform in their denial of any pathologic change in either cardiac or smooth muscle and contrast this to the occasional severe myositis of striated muscle There were a few exceptions, however Weigert (1901)[4] mentioned collections of cells infiltrating the myocardium but wrongly reported them as metastatic tumor Buzzard[5] noted the presence of lymphorrhages in the myocardium of two of his five cases of myasthenia gravis. Similarly, in 1925, Bouttier et al[14a] described considerable cardiac muscle edema and fiber dissociation with interstitial chronic inflammation in one report.

The distinction between the effects of myasthenia gravis on skeletal and cardiac muscle was seriously questioned by Brem and Wechsler in 1934[9] and Barton and Branch in 1937[8] They described cases of myasthenia gravis with varying degrees of striated muscle necrosis, Zenker's waxy degeneration and severe acute and chronic inflammatory reaction Their most striking finding was the presence of almost identical lesions in the myocardium of parallel degrees of severity with the same reactive inflammatory exudate Both cases of Brem and Wechsler had thymomas in addition.

The first investigators to suggest that myocardial necrosis with myocarditis might be an integral part of the pathology of myasthenia gravis were Rottino and his associates in 1942[14] They reported a case with thymoma showing diffuse myocardial necrosis and a similar severe myositis of the striated muscles Carefully surveying all cases of myasthenia gravis with reported necropsy findings since 1901, they found that in a large proportion of these reports the heart was either not mentioned or was described as grossly normal without microscopic confirmation In the occasional random section of the heart routinely taken for histology, the scattered focal nature of the myocardial lesion in the less severe cases

might have made it easily overlooked. Giordano and Haymond in 1944[11] reported a case of parallel myositis and myocarditis in myasthenia gravis with thymoma almost identical to the case of Rottino et al.



Fig 3 Heart in myasthenia gravis with thymoma Note the hemorrhagic mottling of the left ventricular septum, indicating an underlying myocarditis

Russell's[15] careful study of the striated muscle lesions included the cardiac musculature when available. She was able to demonstrate the type I changes in the myocardium of at least three of the six cases studied, and she concluded that the myocardium might be a site of significant pathology in this disease. Mendelow and Genkins[12] found myocardial necrosis with inflammatory reaction in five of their twelve cases, particularly in those associated with thymoma They commented on the parallelism of the degree of striated muscle and myocardial changes in these cases[12,20] This series now consists of 25 postmortem examinations in myasthenia gravis and/or thymoma, of which seven (28 per cent) display

Fig 4 Myocardium in myasthenia gravis Minimal focal necrosis with inflammatory reaction. Note the similarity to Figure 1 x 280

Fig 5 Myocardium Same case as in Figure 3 Severe diffuse carditis with fragmentation of myofibrils x 133

in this series In a parallel group of thymomas surgically removed at The Mount Sinai Hospital, twenty-five per cent were in myasthenics

It is now generally accepted that thymoma may be found in about 15 per cent of all patients with myasthenia gravis.[44 45] Another 65 per cent display some histologic abnormality of the thymus gland of a non-neoplastic nature The exact form of this histologic change is to be discussed below. About 70 per cent of all thymomas seen at the Mayo Clinic have been found in association with clinical myasthenia gravis[34]

Most of our present-day knowledge with regard to the structure and function of the normal thymus gland and its development is a direct result of investigations into the relationship of the thymus to myasthenia gravis Sloan in 1943[46] studied 350 thymuses removed at necropsy in cases of varying age and clinical status. An attempt was made to establish criteria for detecting abnormalties of the thymus in ten operative specimens from patients with myasthenia gravis Hammar in 1926 and 1929 (cited by Boyd[47]) examined 350 normal thymuses from cases of sudden death and over 800 in various diseases. One hundred thymuses in other conditions as well as ten fetal thymuses were studied by Murray and McDonald.[48] Iverson in 1956,[49] in a critical re-evaluation of the thymoma problem, reviewed 165 postmortem thymus preparations from embryos of two to six weeks and fetuses from four weeks to three months gestational age.

A summary of these findings with respect to the normal thymus may prove helpful to the understanding of changes in this gland described in association with myasthenia gravis.

Embryology and Histology of the Normal Thymus

The human thymus gland arises as a paired ventral outgrowth of the third pharyngeal pouches in close association with the lower parathyroid glands late in the sixth week of embryologic development. The cleftlike lumina of these outgrowths are soon lost and the solid tissue masses increase rapidly in bulk at their lower ends Simultaneously, they migrate downward into the anterior mediastinum, losing their connection with the pharynx The paired structures become closely adherent to each other but never completely fuse The right and left lobes of the thymus are usually easily separable.

The thymus in its earliest form is a completely epithelial organ composed of cords and masses of closely packed polygonal cells with a vascular stroma. During the third month there is an abundant ingrowth of mesenchymal tissue which isolates the epithelial components and forms them into lobules. At about this time tight whorls of epithelial cells develop. Their centers fuse into eosinophilic, amorphous masses around which the epithelial cells become wrapped in onionlike, concentric layers.

These are the structures which persist in the adult thymus as the well-known Hassall's corpuscles

Late in the third month there occurs a rapidly increasing colonization by cells which are indistinguishable from the normal lymphocyte The original epithelial gland is thereby converted to the predominantly lymphoid organ seen in postnatal life

The final stages of development produce the characteristic lobulated gland found in the newborn Each lobule has a dense cortical layer of closely packed lymphocytes which is sharply demarcated from a more loosely constructed medullary portion The medulla also contains a scattering of lymphocytes, but here the pale epithelial cells are found in greater numbers These have large vesicular nuclei and are isolated as single cells or in syncytial masses without apparent cell boundaries The medulla also contains the Hassall's corpuscles which are undergoing secondary hyalinization and calcification These vary markedly in number, distribution and degree of degenerative change from gland to gland and even in different areas of the same specimen.

Involution The thymus in the newborn infant practically fills the entire anterior mediastinum The organ continues to grow in size, reaching its maximum total weight at about puberty, although at puberty, it is smaller and less prominent in relation to the other structures of the mediastinum McEachern[50] notes that the maximum size of the thymus when compared to the total body weight is reached during the last few months of fetal life.

The process of physiologic involution of the thymus begins approximately at puberty The previously solid lobules of thymic tissue become more and more separated by an ingrowth of loose connective fatty tissue

distinct until involution is almost complete. The epithelial cells of the medulla diminish in size and number They take on a spindle shape or fusiform appearance, becoming difficult to distinguish from young fibroblasts or recticular cells Hassall's corpuscles also decrease in number and become hyalinized or calcified. The completely involuted gland is represented by masses of fat in the anterior mediastinum preserving the shape of the original gland and containing scattered islands of cellular thymic tissue

At any time during the growth of physiologic involution of the thymus a second process may take place This is known as "accidental or illness involution" It consists of a marked change in the size and histology of the thymus in response to a wide variety of illnesses or nonspecific injuries Selye[51] has shown in the experimental animal that this is an integral

part of the "stress phenomenon" and does not occur in the absence of adrenal cortical tissue. Accidental involution begins a few hours or days after injury and consists of a rapid loss of the lymphocytic elements of the thymus, especially the cortex. The fibrous stroma and the epithelial elements are relatively unaffected No increase in the rate of fat deposition is noted, but fibrosis and atrophy of the gland as a whole does occur

Changes in the Thymus in Myasthenia Gravis

Bell in 1917,[32] Norris in 1936 and 1937,[33] etc, emphasized the finding of "hyperplasia" in those thymuses not actually involved by tumor formation This observation was based on the gross appearance and size of the thymus, and any histologic changes in the gland were not studied extensively. Involution of the normal thymus gland was thought to be virtually complete by adult life, and the finding of any quantity of thymic tissue in these patients was considered distinctly abnormal

It became obvious that a study was indicated of the condition of the normal thymus at any age and in association with illnesses not related to myasthenia gravis. Hammar's (1926, 1929) (cited by Boyd[42]) statistical studies, as graphically illustrated by Castleman and Norris in 1949[43] and 1955,[44] demonstrated an extremely wide range of normal weights and proportions of glandular tissue in all thymuses as well as the degree of involution at any age Castleman pointed out that this variation is so extreme as to nullify the value of most of the statements in the older literature with regard to "thymic hyperplasia" as a pathognomonic feature of myasthenia gravis. It was demonstrated that in the great majority of cases the recorded figures of weight and size fall within the range of normality established by Hammar's findings This is not to deny that changes do exist in the thymus associated with myasthenia gravis, but these are rather of a histologic nature.

It is now well known that the process of thymic involution is never really complete. Sloan in 1943[46] noted that some surviving thymic tissue can be found in any person whatever his age, nature or duration of illness Many cases of myasthenia gravis have been reported in which microscopic examination of thymic tissue has not been carried out because of the erroneous impression that complete involution has occurred In investigating the condition of the thymus in an individual case of myasthenia gravis the possibility of ectopic locations of thymus or even thymic tumors in the neck or mediastinum should also be considered

Lymphoid hyperplasia is the most prominent histologic change in the thymus associated with myasthenia gravis. This is characterized by an increase of lymphocytes in both the cortex and medulla. Its pathognomonic feature consists of the formation of "germinal centers" in the

medullary portion of the gland These are identical to their counterpart

cytes The center appears paler in contrast to the surrounding lymphocytic zone due to the larger, more vesicular nuclei and more abundant cytoplasm of its cells Mitotic figures are noted in the central portions and many phagocytic cells are present

Sloan in 1943[46] observed these medullary lymphoid follicles or germinal centers in seven out of ten operative specimens of thymus removed from cases of myasthenia gravis A comparative study showed that similar lymphoid follicles were extremely rare in normal thymuses. Only an occasional one was found in 14 of the thymuses from 150 cases of sudden death. The rarity of thymic lymphoid follicles in other conditions was also pointed out by Murray and McDonald,[48] Bratton,[39] Reid[42] and others

In a study of the thymus in 35 patients with myasthenia gravis, Castleman and Norris in 1949[43] found medullary lymph follicle formation in 25 (71 per cent) Ten of these 35 patients also had thymomas, with lymphoid follicles being found in the surrounding normal thymic tissue beyond the capsule of the tumor Lymph follicle formation has been noted in five subinvoluted thymuses in The Mount Sinai Hospital postmortem series, as well as in two additional thymuses removed surgically for therapy in myasthenia gravis Other investigators, including the author,[12,13,20] have found similar germinal centers within the thymic tumor itself in some cases associated with myasthenia gravis (see figs 13, 15) Castleman and Norris[43] were able to separate their nontumorous thymuses into three groups according to the number of lymphoid follicles in the medulla and the degree of involution In group I the medulla was so packed with these germinal centers that the cortex seemed compressed by them and formed a pseudocapsule, with a sharper separation from the medulla than that seen in the normal thymus This corticomedullary boundary could be further defined by an increased number of argyrophilic reticulin fibers in this zone

Castleman in 1955[44] stated that 68 per cent of patients with this condition have abnormal thymuses exclusive of tumors These are characterized by varying numbers of lymphoid follicles in the medulla No correlation was found between the numbers of these lymphoid follicles and the clinical course of the myasthenia gravis, although those patients with fewest follicles in the operative specimen seemed to have a poorer prognosis for improvement after thymectomy Ringertz in 1931[13] felt that he could clinically delineate a group of four young females on the basis of their thymic changes in his series of 27 cases All had severe myasthenia gravis

of short duration and rapid progression All showed complete absence of involution of the thymus, with lymphoid hyperplasia and germinal centers in the medulla

Similar lymphoid follicular hyperplasia has been noted in the medulla of the thymus in 66 of 70 cases of myasthenia gravis operated upon by Keynes and studied by Bratton in 1948.[19] Reid[42] in the same year reported these changes in four of six operations, Ringertz[13] in twelve of eighteen cases and Bergh[36] in seven of ten cases. Several of the above authors comment that the lymphoid follicular hyperplasia is apparently limited to the thymus in myasthenia gravis and that none of the other lymphoid organs such as the spleen or lymph nodes display a similar pattern This is in sharp contrast to the generalized lymphoid hyperplasia so characteristic or hyperthyroidism or Addison's disease.

Another notable histologic feature of the thymus is the relatively lesser degree of involution in the glands of myasthenic patients as a group when compared with the normal for their age and sex When one considers the extreme involution of the thymus associated with other diseases as an expression of the "stress" phenomenon, this finding becomes even more striking. The patient with myasthenia gravis may be quite gravely ill, yet the thymus appears somehow resistant to the expected involution. The lymphoid follicular hyperplasia described above is also most prominent in those glands showing the least involutionary change.

An interesting feature of these histologic changes of the thymus is that they are not completely specific for myasthenia gravis but are found in relation to certain other endocrinologic disorders. McEachern[52] points out that Addison's disease, acromegaly, hyperthyroidism, gonadal hypofunction and myasthenia gravis are all associated with muscular weakness or asthenia, all may display creatinuria and all are related to some form of thymic hyperplasia These thymic changes are usually most prominent in hyperthyroidism, which is closely related to myasthenia gravis in a number of clinical and pathologic features Sloan in 1943,[46] in a comparative study of the histology of the thymus in various conditions, notes that involution of the thymus is strikingly retarded or absent in Addison's disease, acromegaly and hyperthyroidism In seven cases of Addison's disease he found three with follicular lymphoid hyperplasia of the thymus comparable to that seen in myasthenia gravis and one with a well-defined thymic tumor. In five cases of acromegaly a diffuse lymphocytic increase was observed together with a prominent absence of any involutionary changes. Similar lack of thymic involution was noted in eighteen of twenty cases of hyperthyroidism, and five of the eighteen showed lymphoid follicular hyperplasia of the medulla as in myasthenia gravis.

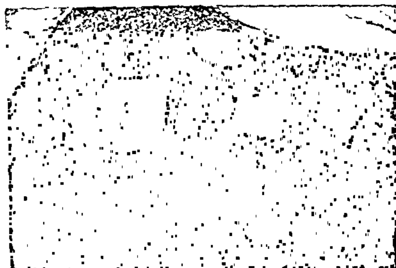


Fig 6. Thymus in myasthenia gravis Absence of normal involution is seen together with lymphoid follicular hyperplasia x 53



Fig 7 Thymus in myasthenia gravis Here, involution has occurred but the remnants of thymic tissue still show lymphoid follicles x 53

The Thymoma

Perhaps more than any other type of neoplasm, tumors of the thymus gland have been the subject of numerous confusing attempts at classification.[45,53,55] The situation appears to have arisen from the fact that every tumor of the anterior mediastinum has at some time been included in these classifications, on perhaps no sounder a basis than close proximity in location to the thymus gland. Dermoid cysts, teratomas, seminomatous tumors of the mediastinum or embryonal cell carcinomas have all been called "thymic carcinomas." Bronchogenic carcinoma or other neoplasms metastatic to the anterior mediastinal lymph nodes have at times been mistakenly considered to be thymic neoplasms

Adding to the confusion is the tendency of the thymus as a partially lymphoid organ to participate in any generalized or multicentric lymph node disorder, such as lymphoid hyperplasia, lymphosarcoma or even Hodgkin's disease These lesions may even arise primarily in the thymus and exist as an isolated focus for some time, but they almost always become generalized to the other lymphoid organs before death Such entities as "Hodgkin's type," "granulomatous type" or "lymphosarcomatous type" of "thymic carcinoma" have been unnecessarily added to some of the classifications of thymic tumors.[54,55] These diseases exhibit no known clinical differences from their counterparts in other lymphoid organs None of the "tumors" of the thymus known to be of lymphoid origin have ever been found in association with myasthenia gravis. This lack of association is also true for the other tumors of the anterior mediastinum listed above.

Bell in 1917[32] was one of the first to define the thymoma as a "tumor, benign or malignant, probably derived from thymic epithelium and usually identifiable by (the presence of) epithelium and lymphocytes Hassall's corpuscles are sometimes present." Bell was of the opinion that the thymomas found with myasthenia gravis were a distinct group unlike any other thymic tumors Norris'[33] viewpoint was even more extreme. He felt that the thymoma was not a true neoplasm, but rather an extreme form of epithelial hyperplasia in association with myasthenia gravis In view of the occurrence of thymomas in the absence of myasthenia gravis and the malignant potentialities of at least some of these tumors, the neoplastic nature of the thymoma can hardly be doubted.

The thymoma usually is found in the anterior mediastinum corresponding to the position of the thymus, and many possess a rim of normal thymic tissue in a manner analogous to other endocrine adenomas. Considering our knowledge of the embryologic derivation of the thymus, it is not surprising to encounter reports of ectopic locations of thymomas in

the neck,[44] the root of the left lung,[44] or even within the right middle lobe pulmonary parenchyma[56] Thymomas vary markedly in size, the smaller ones usually being reported in patients with myasthenia gravis in whom the clinical symptoms usually suggest early x-ray examination for this tumor. In cases without myasthenia gravis, weights of tumor up to 300 grams have been reported.



Fig 8 Thymus in myasthenia gravis, with thymoma replacing one lobe of the gland

A thick capsule encases the thymoma from which dense fibrous septae penetrate the parenchyma, dividing it into lobules of varying sizes. The capsule and septae are often the site of calcification which may produce plaques of sufficient density to be seen roentgenographically This classification was noted in thirteen of forty-five cases (35 per cent) reported by Seybold et al[34] In contrast to other tumors the presence of calcification is not necessarily an indication of a benign nature, calcium deposits having been found in some of the more malignant tumors in The Mount Sinai Hospital series

On section the interior of the thymoma presents a pale gray or pink-white fleshy color with the characteristic fibrous septae and lobulation being easily recognizable grossly. Hemorrhagic changes and yellowish areas of necrosis are a frequent gross feature. Cystic degeneration is often produced by the coalescence of microscopic foci of necrosis and accumulation of secretions. In some cases these changes become confluent and



Fig 9 Thymoma in situ Note the well-defined capsule. This patient also had myasthenia gravis

so extensive as to convert the entire neoplasm into a single thick-walled cyst filled with grumous necrotic material. The original thymoma may be found only as microscopic islands in the wall of such a structure. In extreme examples the thymic origin of the cyst may become completely unrecognizable. This circumstance is exemplified in the cases reported by Blalock et al[35] and by Fulghum[57] in which such mediastinal cysts of uncertain origin were present in patients with myasthenia gravis. Even



Fig 10 Thymoma (same as Figure 9) The lobulation and variation in appearance of different areas is seen



Fig 11 Thymoma Note the thick fibrous capsule and the areas of cystic necrosis nd hemorrhage

more remarkable is the fact that the surgical removal of both these cysts produced remissions in the symptoms of myasthenia gravis in spite of the complete absence of presumably functioning thymus or tumor tissue.

When the thymoma is examined microscopically, it is seen to be a very cellular tumor with a well-defined lobular architecture produced by the thick supporting fibrous septae seen grossly. The parenchyma consists of two cell types similar to those encountered in the medulla of the well developed thymus These are the "thymocyte" or lymphocyte and the "reticular" or epithelial cell. The thymocyte is identical to the lymphocyte

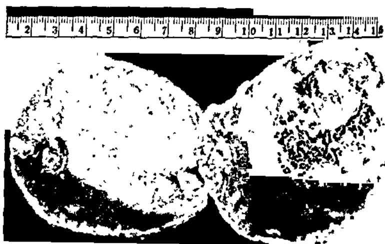


Fig 12 Thymoma, showing complete cystic degeneration and necrosis These are occasionally confused with dermoid cysts of the mediastinum

in morphology and biologic behavior and is considered as a true lymphocyte by most investigators The epithelial cell is characterized by a pale, vesicular, round or ovoid nucleus and variable amounts of granular or vacuolated cytoplasm. The cell border is usually indistinct and the epithelial cells appear as syncytial masses. Mitoses are extremely rare except in the most rapidly growing tumors

Castleman and Norris[13] described three different histologic patterns in thymoma based on the ratio of lymphocytes to epithelial cells Type I is composed mainly of epithelial cells in an irregular network of anastomosing cords or sheets, with sinusoidal capillaries between them producing an adenomatoid pattern. Often the epithelial cells appear to align themselves in a palisaded arrangement, simulating glandular formations

around blood vessels or cystic spaces or along the fibrous trabeculae at the border of the lobule. Scattered lymphocytes are compressed in rows between the cells and concentrated in cuffs around the small vascular channels Type III consists predominantly of lymphocytes with occasional epithelial cells lying isolated or clumped in small syncytial groups among the lymphocytes. Intermediate between these forms is type II which is composed of an approximately equal ratio of epithelial cells and lymphocytes Any one tumor may have lobules exemplifying all three different types, often lying side by side.



Fig 18 Thymoma (with myasthenia gravis), illustrating the lobulation by thick radiating fibrous septae. Note the lymphoid follicles to the right of the field and the Hassall's corpuscle in the center x 53

In one well-defined group of thymomas the epithelial cells are seen to be replaced by a more elongated or fusiform spindle cell resembling a young fibroblast These cells are arranged in whorls or columns, often forming an interlacing network with more cellular tumor areas in the interstices. The same characteristic intermingling of lymphocytes is found in these tumors (see fig 19) Areas of transition from definite epithelial

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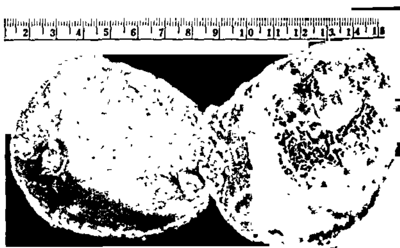


Fig 12 Thymoma, showing complete cystic degeneration and necrosis These are occasionally confused with dermoid cysts of the mediastinum

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Castleman and Norris[43] described three different histologic patterns in thymoma based on the ratio of lymphocytes to epithelial cells Type I is composed mainly of epithelial cells in an irregular network of anastomosing cords or sheets, with sinusoidal capillaries between them producing an adenomatoid pattern. Often the epithelial cells appear to align themselves in a palisaded arrangement, simulating glandular formations

around blood vessels or cystic spaces or along the fibrous trabeculae at the border of the lobule. Scattered lymphocytes are compressed in rows between the cells and concentrated in cuffs around the small vascular channels Type III consists predominantly of lymphocytes with occasional epithelial cells lying isolated or clumped in small syncytial groups among the lymphocytes Intermediate between these forms is type II which is composed of an approximately equal ratio of epithelial cells and lymphocytes Any one tumor may have lobules exemplifying all three different types, often lying side by side



Fig 13 Thymoma (with myasther ... k
radiating fibrous septae. Note the ... u c
Hassall s corpuscle in the center ...

In one well-defined ... seen to
be replaced by a ... mbling a
young fibroblast. T ... ons, often
forming an inter ... areas in the
interstices The ... ytes is found
in these tumors ... finite epithelial
cells to this s ... the necessity of
classifying ... ndle cell type of
thymoma is ... a gravis.

more remarkable is the fact that the surgical removal of both these cysts produced remissions in the symptoms of myasthenia gravis in spite of the complete absence of presumably functioning thymus or tumor tissue.

When the thymoma is examined microscopically, it is seen to be a very cellular tumor with a well-defined lobular architecture produced by the thick supporting fibrous septae seen grossly. The parenchyma consists of two cell types similar to those encountered in the medulla of the well-developed thymus These are the "thymocyte" or lymphocyte and the "reticular" or epithelial cell. The thymocyte is identical to the lymphocyte

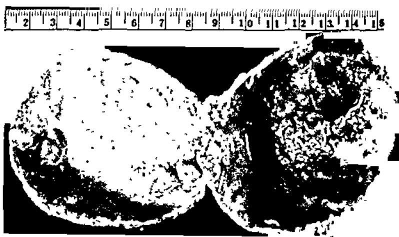


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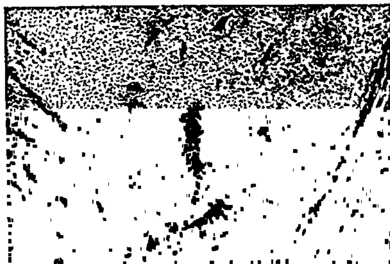


Fig 16 Thymoma (with myasthenia gravis) An almost purely epithelial area A few lymphocytes are present and are clumped around capillaries x 133

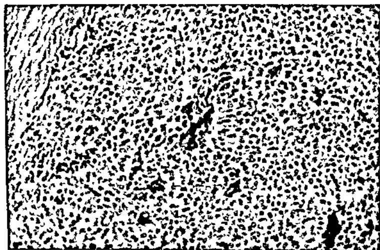


Fig 17 Higher magnification of Figure 16 Note the tendency of the epithelial cells to palisade around the capillaries in a radiating fashion x 280

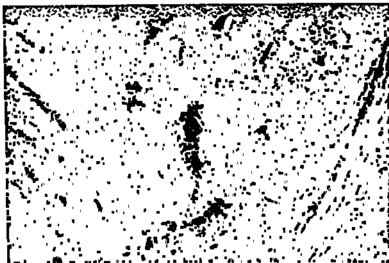


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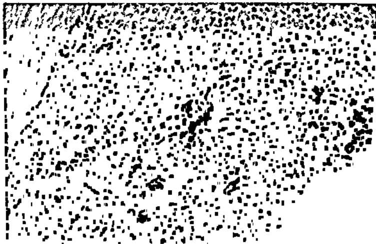


Fig 17 Higher magnification of Figure 16 Note the tendency of cells to palisade around the capillaries in a radiating fashion. x 250

The origin of the thymoma as a tumor of the thymus gland is furt attested to by the finding of definite Hassall's corpuscles in about 25 to per cent of cases [13,20,31,48] These range from ill-defined whorls of epithe cells to calcified, hyalinized, eosinophilic bodies identical to those seen normal thymus (see fig 18).

In most reviews of the pathology of thymoma, it is stated that no d nite histologic pattern exists in these tumors that may be correlated w the presence or absence of clinical myasthenia gravis to any degree accuracy. However, Castleman [44] feels that certain features when c sidered as a group enable him to predict the relationship to myasthe gravis in about 75 per cent of cases. The presence of epithelial cells w plump vesicular nuclei arranged in an adenomatoid pattern with ly phocytic cuffing of capillaries tends to support the diagnosis of myasthe gravis. In contrast, the predominantly lymphocytic tumor and especia the spindle cell variant of thymoma are rarely encountered in this disea

Iverson in 1956 [49] in a review of thymomas felt that she could demo strate gross and microscopic features characteristic of myasthenia gra in 13 of a series of 27 cases (48 per cent). The main histologic criteri appears to consist of a loose association of lymphocytes with large, wate pale epithelial cells in a succulent vascular bed with little fibrous stron The relative proportion of lymphocytes appears to have little clinical s nificance In areas where lymphocytes are scant the epithelial cells ta on an almost syncytial arrangement. Both Iverson and Castleman menti the presence of periodic acid–Schiff-positive granules finely dispers throughout the cytoplasm of these cells The spatial relationship to thi walled blood vessels is described as being of particular significance. Ive son feels that these features bear a close resemblance to the histology an endocrine gland and tend to suggest an endocrine-like function for t epithelial cells described above.

Malignancy of Thymomas One of the most unique attributes of t thymoma aside from its relationship to myasthenia gravis is its "limite degree of malignancy as a tumor. This term refers to the fact that amon the many hundreds of true thymomas described in the literature up the present, there exists no substantiated case of spread outside th thoracic cavity by lymph node or blood-borne metastasis Within th thorax the thymoma displays at least some of the behavior we ascribe malignancy in over 25 per cent of cases. On occasion, these tumors infi trate through their capsules and invade the parenchyma of the adjacen organs, namely, the lung, pericardium or great vessels of the mediastinum Distant separate implants of tumor tissue may be found on the viscer or parietal pleura, pericardium or thoracic surface of the diaphragm. On case is reported by Derow et al.[53] of peripheral metastasis within th



Fig 18 Hassall's corpuscle in thymoma with myasthenia gravis x 280

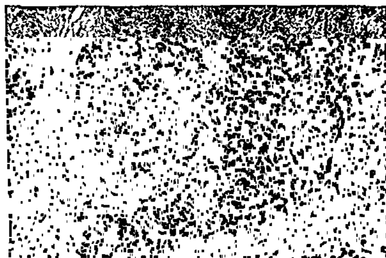


Fig 19 Thymoma, spindle cell variant Note the tendency of the spindle shaped cells to merge with the septae and imitate cellular fibrous tissue The characteristic intermingling of lymphocytes is also seen x 133

The origin of the thymoma as a tumor of the thymus gland is further attested to by the finding of definite Hassall's corpuscles in about 25 to 50 per cent of cases.[13,20,34,45] These range from ill-defined whorls of epithelial cells to calcified, hyalinized, eosinophilic bodies identical to those seen in normal thymus (see fig 18).

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Fig 18 Hassall's corpuscle in thymoma with myasthenia gravis x 280



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lung as a result of aspiration of tumor tissue eroding into a major bronchus Recurrence of tumor growth after apparently complete removal of an encapsulated thymoma is also noted[53]

Histologically, there are few usable criteria for identification of the potentially or actually malignant tumor of the thymus. Mitoses are extremely rare and nuclear atypism or hyperchromatism most infrequent. No reliable histologic differences can be found between tumors of completely benign clinical nature and those with eventual malignant behavior Even the thymoma invading adjacent organs, found as an implant on serosal surfaces or recurring after removal, is microscopically identical to the original tumor.



Fig 20 Invasion of the pericardial sac at the base of the heart by a malignant thymoma associated with myasthenia gravis.

The older literature contained few examples of malignant thymoma seen in association with myasthenia gravis. Only five such cases had been reported up to 1942.[40] It was often stated that only the "benign" thymoma was significantly related to myasthenia gravis,[35] but more recent investi- [illegible] ...ew of the literature, Mor- ... of histologically proven ... died for the presence of ... had clinical myasthenia



Fig 21 Complete encasement of the visceral pleura of the lung by malignant thymoma, with superficial invasion of the subpleural lung parenchyma Note also the infiltration of tumor along the lung fissure This patient also had myasthenia gravis.



Fig 22 Malignant thymoma (with myasthenia gravis) invading the adjacent lung and filling the alveolar spaces x 53

gravis associated with malignant thymoma. The Mount Sinai Hospital series of 26 thymomas found at necropsy or removed surgically contained ten examples of malignant thymoma judged by the criteria described above. Seven of these were also associated with clinical myasthenia gravis.

Causes of Death in Myasthenia Gravis

One of the most unusual and yet characteristic aspects of myasthenia gravis is the sudden and often unexpected occurrence of death in a patient who seems to be making a satisfactory adjustment to his disease. Rowland et al.[3] describe sudden acute myasthenic attacks fatal within a few minutes to an hour in 13 of 39 patients dying. Even among 16 other patients already in a respirator at the time of death, the final critical change was sudden and unforeseen in eight. It should be pointed out that practically all 39 cases had severe generalized myasthenia gravis when they died.

When one excludes those cases dying postoperatively following removal of a thymoma or thymectomy, and those due to some difficulty with drug management precipitating cholinergic or myasthenic crisis, one finds that the extent of pathologic changes in the vital organs seen at autopsy is sometimes hardly sufficient to be considered as the cause of death. Pulmonary pathology is a practically universal necropsy finding in myasthenia gravis and is especially prominent in those patients dying in a respirator. Bronchiolitis is noted, with excessive production of mucus which undergoes inspissation and causes bronchial obstruction and focal atelectasis. Congestion and edema are also frequently observed, occasionally accompanied by hydrothorax. In many cases, however, the pulmonary pathology may be minimal.

In view of the myocardial necrosis with reactive myocarditis described in some cases of myasthenia gravis, it has been suggested that a cardiac mechanism may be responsible for sudden death. Even minor lesions in the myocardium may give rise to a vagal reflex resulting in cardiac arrest or ventricular fibrillation. The associated hypoxia of respiratory insufficiency as well as the drug therapy being employed may facilitate the development of this reflex.

The brain usually reveals only the effects of severe acute hypoxia in those cases with difficulty in aeration. These changes include focal perivascular hemorrhage and necrosis with nerve cell degeneration, particularly in the brain stem and basal ganglia.

One is forced to conclude that even the final cause of death in myasthenia gravis, especially in those cases which suddenly enter the terminal state, cannot always be explained satisfactorily on the basis of the patho-

logic findings alone, adding another factor to the many mysteries still surrounding the etiology and pathogenesis of this disease.

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CHAPTER III

Physiology

THE ETIOLOGY of myasthenia gravis has not yet been demonstrate *understanding of the physiology of neuromuscular transmission an* resultant muscle contraction is essential to an evaluation of the dat tained in the study of the myasthenic phenomenon Because in ma its aspects, particularly in therapy, a major disorder of neuromus (myoneural junction) transmission seems to be present when the r thenic syndrome is observed, particular emphasis will be given this of neuromuscular activity. It should be remembered that muscular ac is the result of a series of events which involve the nervous syster the periphery these include: (a) the passage of nerve impulses dow motor fiber and through its terminal arborization; (b) transmission o impulse from the nerve to the muscle at the neuromuscular junc (c) conduction of the impulse along the muscle fiber; (d) active shorte of the contractile elements of the fiber, and, (e) reconstruction of entire system so that additional impulses can occur.

NORMAL NEUROMUSCULAR TRANSMISSION

The ability to move about is dependent upon an intact nervous sys neuromuscular junction and muscle. Biologic integrity of the mu fiber is dependent upon the integrity of its innervation. After motor de vation, structural and metabolic changes develop within the muscle W a muscle is effectively stimulated, simultaneous electrical, chemical thermal changes occur as concomitants of shortening and possibly re tion. The chemical potential energy is converted by the muscle into chanical energy These changes are cyclical and reversible so that muscle can be alternately contracted and relaxed.[1 3]

Loss of the use of muscles to varying degrees may be caused by co tions originating within the muscle, but more often it is caused by of the numerous nervous disorders and at times by transmission diffic at the neuromuscular junction.

Structure of Neuromuscular Junction

The classical description of the neuromuscular (myoneural) junctio a synapse between the motor nerve ending and the muscle fiber. The tor nerve fiber penetrates the sarcolemma of the muscle fiber, at wh

point it loses its myelin sheath and the neurilemma blends with the sarcolemma The axoplasm is in close contact with the sarcolemma and the side facing the muscle fiber is named the terminal (presynaptic) membrane of the axonal end process The subneural space is probably a microscopic gap separating the terminal membrane on one side from the sole plate of Kuhne,[4] which is a modified sarcoplasm of the muscle fiber The postsynaptic or postjunctional membrane is the side of the sole plate facing the terminal membrane [5,7]

Electronmicroscopic studies [8,9] reveal several points of difference from the above description

1 There is no cytoplasmic continuity between the presynaptic axonal ending and the sarcoplasm

2 The sarcoplasmic cell membrane is indented by the axonal endings to form a trough in which the latter lies

3 Near and within the synaptic troughs, the muscle membrane complex (sarcolemma) is thrown into deep folds which branch and anastamose in a complex fashion (This is probably identical with the subneural apparatus of Koelle [10] and Couteaux [7])

4 The external surface of the axonal endings continues to be covered by cellular elements of the Schwann sheath which separate the axoplasm from the extracellular space and which are definitely distinct from the sarcolemma

5 The cytoplasm of the axonal ending is differentiated from the axoplasm in that it appears to be divested of fibrillar elements, contains a greater number of mitochondria, and appears to be packed with spherical structures which have been termed "synaptic vesicles"

Thus, the synapse consists of three parts terminal membrane, subneural space and postjunctional membrane, although this description is a simplification since the junctional region is multicellular and the role of all the cells participating in it is not clear

Biophysics of Normal Neuromuscular Transmission

The mechanism through which the muscle is stimulated by the motor nerve has been under investigation for the past few decades As early as 1904, Elliot [11] suggested that the sympathetic nerve endings liberate adrenalin which acts as a chemical mediator of the nerve impulse upon the effector cell The work of Loewi,[12] Dale,[13] Feldberg,[14] Nachmansohn [15] and others ascribe a similar role to acetylcholine in the transmission of nerve impulses from parasympathetic nerve endings to effector cells In 1933, Dale and his associates extended this hypothesis to include transmission of nerve impulses across the neuromuscular junction and ganglionic synapses This concept of neurohumoral transmission seemed



Fig 23 Electron micrograph of an ultrathin section of mouse intercostal muscle, showing a portion of a neuromuscular junction The extracellular space is at the top of the figure, the cytoplasm of the myofibril at the bottom. The axonal ending (limited by the axonal membrane "a m") is seen lying in the synaptic trough, the surface facing the extracellular space is covered by a Schwann cell "sch c." The actual synapse (one portion of which is delimited by arrows) is composed of the axonal membrane "a m," (prejunctional) the muscle plasma membrane or sarcolemma "m p m" postjunctional and the intervening space (subneural space) The muscle plasma membrane is thrown into a complex series of "junctional folds" "j f," which are cut transversely at the left of the figure and tangentially at the right. Mitochondria "m" and synaptic "vescicles" "s v." are seen in the cytoplasm of the axonal ending Portions of two sole plate nuclei "s p n" appear at the bottom of the figure Magnification x 25,000 (Courtesy of Dr G M Lehrer)

necessary in order to interpret and reconcile the findings based on electrical studies. Feldberg became the exponent of the chemical-electrical theory in which depolarization of the endplate is said to be caused by acetylcholine which is elaborated at the terminal membrane of the motor nerve and then diffuses through the subneural space to reach the [illegible] junctional [illegible]
tr [illegible]
a [illegible] terminal membrane which jumps the few millimicron-wide gap of the subneural space This electr[illegible] liberates [illegible]
c [illegible]
h [illegible] conducting membrane of the muscle and leading to increased ion permeability It forms an integral part of a system by which bioelectric potentials are generated in the axon, in the nerve terminal and in the postsynaptic membrane The propagating agents along the axon and across the synapse are changes in electrical potential difference. With the change in permeability of the muscle membrane,



potassium moves out and sodium moves into the muscle fiber. This explanation accords with all the modern theories postulated for nerve impulse conduction.[18]

Feldberg[14] has shown that acetylcholine is responsible for the transient change in permeability and that it must be rapidly inactivated, otherwise a series of contractions could not occur. This inactivation is accomplished by the hydrolysis of acetylcholine through a specific enzyme, acetylcholinesterase, which has been shown by Ravin,[19] Denz,[20] Koelle,[10] and Lehrer[21] to be present at the neuromuscular junction about the palisade like "subneural apparatus" of the endplate. The outstanding feature of the enzyme is the high speed at which it accomplishes its work. This satisfies a prerequisite of associating a chemical reaction with electrical manifestations The acetylcholine is broken down into its component parts of acetate and choline which are then resynthesized into acetylcholine by another specific enzyme, choline-acetylase[18]

The physiologic studies of Fatt, Katz, del Castillo and co-workers,[22-24a,b] have suggested the probability that the release of acetylcholine from the nerve endings occurs in discrete "quanta," each of which gives rise to a miniature endplate potential. A property of acetylcholine quanta is their constancy during a variety of experimental changes, meaning that the size of the quanta remains stable whether the release takes place spontaneously at infrequent intervals or in a momentary synchronous burst after the arrival of a nerve impulse No agent has yet been found to have a demonstrable effect on the size of the transmitter quantum[24a] Acetylcholine may be contained within the nerve endings in structural parcels (possibly the synaptic vesicles), from each of which it is discharged in an all-or-none fashion.

Nachmansohn, who has demonstrated that acetylcholine appears to act as a prosthetic grouping attached to four different proteins, has investigated the characteristics of this acetylcholine-protein linkage He states that differences in the pharmacologic activity of the organic ammonium compounds appear to be explicable in terms of variations in the nature and site of the protein-acetylcholine "bond."[18]

Muscle Action Potential The resting muscle fiber has a potential difference of approximately 90 millivolts across the surface membrane, with the positive charge being on the outer surface and the negative charge on the inner surface This is a state of polarization The resting membrane potential has been explained as being due to the difference between the intracellular and extracellular concentration of ions Stimulation of the muscle fiber, according to Nachmansohn, either indirectly through its motor nerve or directly by a cathodal current, liberates acetylcholine from protein #1, its bound form The liberated acetylcholine is then adsorbed by

the second protein, the cholinergic receptor of the endplate, which causes a change in its spatial configuration This results in a temporary increase in permeability of the plasma membrane Sodium ions enter from the extracellular fluid while potassium diffuses out, the former exceeding the latter The potential difference between the interior and exterior of the membrane changes so that it decreases to half its resting value. Propagation does not occur until this critical value (45 millivolts) is attained When this critical level is reached, the membrane becomes depolarized, and a current flowing in the localized area affected is produced. This wave of depolarization is propagated along the muscle membrane Acetylcholine is attached to the third protein, acetylcholinesterase, which quickly hydrolyzes it into acetate and choline This restores the membrane permeability to its resting state, causing a reversal of the above-described ion flow, and repolarization is accomplished This propagating wave of

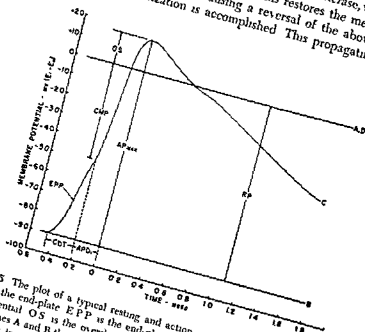


Fig 25 The plot of a typical resting and action potential record obtained at the center of the end-plate E P P is the end-plate potential C M P is the critical membrane potential O S is the overshoot The line B is the resting membrane potential level In lines A and B the microelectrode is outside the fiber, and in line C the microelectrode is inside the fiber The resting membrane potential is −90 millivolts, the critical level is at −45 millivolts When this critical level is reached, the potential change is termed the action potential, which becomes propagated and overshoots to an electropositive phase This is followed in a few milliseconds by repolarization of the end-plate Reprinted, by permission, from W L Nastuk Am J Med. 19 663, 1955

depolarization and polarization is known as muscle action potential.[27,28] Nastuk[28] has shown that depolarization can be almost completely prevented if sodium chloride is removed from the extracellular fluid. Finally, the fourth protein, cholineacetylase, reconstitutes the acetate and choline to acetylcholine, returning the neuromuscular junction to its resting state.

There are constantly recurring minute potentials which are localized *and nonpropagating and which are said to be due to subliminal amounts* of acetylcholine.[23,25] When a nerve impulse reaches the endings in the neuromuscular junction, a potential difference is created at the postsynaptic membrane.[29] This potential is termed the endplate potential and differs from the propagated nerve or muscle impulse in several distinct ways.

1. It has been shown to consist of spatially and temporally summated miniature endplate potentials.[25a]

2. It is associated with the release of acetylcholine. (According to Nachmansohn, this release is beyond the junctional membrane. See above.)

3. It is not propagated along the membrane surface.

4. In physiologic experiments, successive endplate potentials delivered prior to the decay of the previously occurring one, are additive (summation). When the endplate potential is of sufficient amplitude, depolarization of the muscle membrane occurs and a propagated impulse results along the muscle fiber. This wave of depolarization along the fiber membrane is then followed by shortening of the contractile elements.[30] The endplate potential is, therefore, an electrotonic rather than an all-or-none phenomenon.

5. Acetylcholine when applied externally to the endplate causes depolarization. No such effect can be produced by its application to the muscle, even at much greater concentrations.

Motor Unit. Anatomically, it has been shown that each nerve fiber innervates a varying number of muscle fibers. In the small muscles, such as the extraocular muscles, the ratio is one to five, in large skeletal muscles the ratio may be one to two hundred. A motor unit consists of a motor neuron and the muscle fibers which it innervates. Since excitation of each axon or muscle fiber is of an all-or-none type, a motor unit normally responds to a single stimulus in an all-or-none manner. When a motor nerve containing several motor axons is given a single electrical stimulus of sufficient strength and duration, a single muscle twitch is elicited. With increasing strength of the stimulus, more axons and more motor units respond, so that maximal stimulus apparently excites all the nerve fibers and, therefore, all the muscle fibers supplied by the motor nerve. Any increase in stimulus beyond this produces no increase in muscle contraction since all the motor units are already being activated.

When the nerve is stimulated maximally or supramaximally, the amplitude of the integrated action potential is a function of the number of muscle fibers responding to the nerve stimulus This fact is used in electromyography by recording the muscle action potential produced by placing an electrode within the muscle or on the skin overlying the muscle [25] The relationship between electrical and mechanical response is not completely predictable However, Wagman and his co-workers [77,79] have shown that under certain conditions a greater than maximal response, both electrical and mechanical, can be obtained This suggests that there is a factor of safety in muscle function and that not quite all fibers contract in response to a maximal stimulus or effort

Neuromuscular Block A disturbance of the normal sequence of events at the neuromuscular junction causes an interference with neuromuscular transmission which is commonly known as neuromuscular block (There are some differences of opinion concerning the location of acetylcholine release and resynthesis One view is that acetylcholine is released at the motor nerve termination Nachmanschn's view is that of a universal phenomenon occurring along the axon membrane, postsynaptic membrane and muscle fiber membrane) Grob et al [25] classify the types of neuromuscular block as follows

1 Deficient release of transmitter substance acetylcholine from the motor nerve endings This is probably the mechanism of botulinus toxin poisoning [31] and a severe hypocalcemia in the experimental animal [32]

2 Excessively rapid removal of transmitter (acetylcholine) following its release from nerve endings This postulates an excessive concentration of muscle cholinesterase, which has not been observed or experimentally reproduced

3 Competition block (inhibition of the depolarizing action of the transmitter on the endplate) This may be termed an acetylcholine inhibitory block, of which there are three types

a Block occurring without change in the resting potential of the muscle membrane and reversible by acetylcholine or an anticholinesterase compound D-tubocurarine in experimental animals produces this type of block [33,34] D-tubocurarine is believed to exert its effect by competing with acetylcholine for receptor sites at the endplate This has been termed a competitive block, and it has the following characteristics·

i It is not preceded by an increase in motor activity

ii In response to two or more nerve stimuli, there is a progressive decline in the muscle action potential D-tubocurarine does not affect the output of acetylcholine from the motor nerve ending The assumption is that the decline in muscle response to repetitive nerve stimuli reflects variations in the amount of acetylcholine normally liberated [35,30] When

there is no block, such a decline does not exist inasmuch as the decreasing amounts of acetylcholine liberated with repetitive stimulation are still sufficient to give maximal stimulation With curarization the threshold of the endplates to the stimulating action of acetylcholine is raised, thereby revealing the progressive decline in the amount of acetylcholine released with repeated nerve stimulation.

iii. Post-tetanic facilitation. After tetanic stimulation there is an increase in the muscle action potential response to a single nerve stimulus. Smith et al [34] and Hutter [35] have indicated that this facilitation is due to *increased acetylcholine output from the nerve endings as reflected* in the endplate potential When a series of stimuli is given after a tetanic stimulation, the response of the first stimulus of the train is facilitated (increased), but subsequent responses are of lower amplitude. Liley and North [36] claim that at this point there is decreased output of acetylcholine from the nerve endings.

iv Van Maanen [33] states that there is a decrease in the depolarizing action of acetylcholine or anticholinesterase compounds.

v Competitive block is reversed by the injection of sufficient acetylcholine or anticholinesterase compound.

b Block not associated with any change in membrane potential, but not reversible by acetylcholine In frog nerve muscle, prolonged exposure of an endplate to acetylcholine causes at first a depolarization and then a later recovery of the membrane resting potential. Despite the recovery of the membrane potential, neuromuscular block persists.[37 39]

c. Block associated with hyperpolarization of the membrane, which may be the type of block seen in periodic familial paralysis [40]

4 Depolarization or cholinergic block: abnormally prolonged depolarization in the region of the endplates. When the endplate is depolarized it becomes inexcitable to further stimulation Depolarization can be produced by excessive concentration of acetylcholine,[41,42] by anticholinesterase compounds, and in most animal species by decamethonium [42] or choline.[43] Depolarization block has the following characteristics·

a Before the block there is an increase in motor activity induced by the initial endplate depolarization

b Two or more nerve stimuli produce no progressive decline in the muscle action potential, with the exception of the block following anticholinesterase compounds in which case the accumulation of acetylcholine causes intensification of the block following each stimulus.

c. There is no post-tetanic facilitation.

d Injected acetylcholine or anticholinesterase compounds have an additive effect.

e. Depolarization block is reversible b ,[4] ' ction of competitive

block agents such as d-tubocurarine, but not by acetylcholine or anticholinesterase compounds Noncompetitive neuromuscular block which is neither nonacetylcholine-inhibitory or reversible is frequently presumed to be of a depolarizing type But demonstration of this mechanism requires measurement of the membrane potential in the region of the end-plate, which as yet has not been carried out in man

5 Mixed type block. The precise classification of neuromuscular block may be difficult because of the appearance of properties of more than one type or because of the change in the type of block with time Zaimis[44] has shown that decamethonium administered to the monkey, dog or rabbit has the property of a competitive block but is preceded by an initial increased motor activity suggestive of depolarization block Jewell[45] and Zaimis have shown a differentiation between the response of the red and white muscles of the cat in their response to decamethonium The pale muscles respond in a depolarizing manner, whereas the red muscle is initially depolarized and then shows a competitive block

PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS

The modern era in the study of myasthenia began about 1935 with the neurohumoral theory of Loewi and Dale and the realization that myasthenia gravis, which clinically resembles curare poisoning, could be reversed by eserine and later by Prostigmin[46] Three lines of study resulted from these observations (1) a comparison was made of this process with normal processes and with the blocking effects of curare and other agents by electromyographic means, (2) efforts were made to discover a circulating toxin, curare-like in nature, especially directed toward the thymus gland as a source, and (3) new drugs having anticurare or anticholinesterase activity were studied as therapeutic agents[47]

The junctional transmission of nervous effects by chemical agents, especially that of Prostigmin, concentrated attention on the neuromuscular junction[48] The fact that Prostigmin is an anticholinesterase drug had led to frequent discussion in the contemporary literature of two possible abnormalities at the neuromuscular junction in myasthenia gravis, namely, increased cholinesterase activity and diminished production of acetylcholine Since Prostigmin is effective, it is obvious that it would correct either one of these abnormalities if they existed, but there is no conclusive evidence to suggest that either does in fact exist,[49, 49a]

No abnormality has been found in the true or pseudo cholinesterase content of the blood or muscle in the myasthenic patient Measurements of the quantitative amount of acetylcholine formed at the neuromuscular

junction in myasthenia gravis have not yet been made, but this information will subsequently help to clarify the physiology of this syndrome.

There is interesting evidence that some metabolite, a curare-like substance, is present at the neuromuscular junction in myasthenia gravis. If the circulation of an extremity is occluded by a tourniquet at a time when a myasthenic patient shows no evidence of ptosis and the occluded extremity is then exercised, on release of the tourniquet and the passage of the blood back into the general circulation, the eyelid will occasionally become ptosed This is the so-called Walker effect.[50] This phenomenon has been observed by me only on rare occasions.

As a consequence of Walker's report, many investigators have drawn blood from an exercised ischemic limb in the hope of increasing the concentration of neuromuscular blocking agent in the sample. Hypoxic exercised muscles release many metabolic products, some of which might have a mild depressant action on neuromuscular transmission "Such subliminal inhibition might be difficult to detect in a normal individual whose neuromuscular transmission has a large safety margin But in the myasthenic patient, the neuromuscular transmission process has little or no safety margin, and for this reason, it is easily interrupted by inhibitory influences which for the normal individual would be classed as subliminal"[51]

Wilson and Stoner[52] have tested on a nerve-muscle preparation the effect of serum withdrawn before and after exercise from patients with myasthenia gravis during occlusion of the circulation The serum produced a curare-like lowering of the height of the contraction to nerve stimulation, with a slight effect (not greater than 25 per cent) before exercise, but a pronounced depression of responses after exercise, amounting *in some cases to complete blocking of neuromuscular transmission* Nastuk et al,[51] citing a personal communication from Wilson, stated that the positive results in 11 of 13 cases showed a loss of tetanus tension averaging 20 to 25 per cent of the control value

Struppler[53] emphasizes the importance of exercise under ischemic conditions and increasing the concentration of a humoral neuromuscular blocking agent He presents experiments that absolve the products of an *anaerobic muscular activity as a causative factor for inhibition* of neuromuscular transmission, but these conclusions have been questioned because of the amount of d-tubocurarine which was administered in his studies.[51]

Nastuk et al[51] found no evidence to support the view that exercise under ischemic conditions increases the neuromuscular blocking action of plasma obtained from the involved arm They state that the experiments should not be regarded as providing critical evidence on this ques-

tion because of the small number of controlled comparisons which were made.

Lammers[54] used the serum of three myasthenic patients in whom anticholinesterase medication had been stopped for twenty-four hours. The serum was examined within two hours of sampling. This serum was tried on many species of animals without demonstration of the presence of a paralytic factor. Schwartz[55] attempted to find the curare-like factor by using transfusion techniques in human subjects, giving 1,500 ml of blood from myasthenia patients with marked symptoms to a normal individual. No weakness was created. Conversely, an exchange transfusion of 4,000 ml of normal blood was given to a myasthenic patient without improvement. Van Maanen[56] cautions that the method for assaying blocking agents may be too insensitive, for it does not detect curare in the serum of an animal fully paralyzed by the drug.

Nastuk et al[57] first tried repeating Wilson and Stoner's experiment and then branched off into other physiologic approaches in an effort to discover the presence of a circulating curare-like substance. Plasma and serum samples were obtained from 22 myasthenia gravis patients and 9 normal controls. Some of the samples were taken after exercise under ischemia. The samples were applied, in various dilutions, to the frog sciatic nerve–sartorius muscle preparation in vitro. The twitch and tetanus tensions of the preparation were measured using indirect stimulation under three different conditions. Samples from 13 of the myasthenic patients caused appreciable augmentation of the twitch or end tetanus tension. Such augmentation was also seen with samples from three of the controls. The causes of this augmentation effect are not known. Samples from five of the myasthenic patients caused a reduction of maximum tetanus tension beyond that produced by the controls. The characteristics of the depression differ from those which would be produced by curare. In addition, the depression is to a large extent irreversible and it involves lysis of surface fibers of the sartorius muscle used in the assay. The relation between the serum depressant activity and the etiology of the disease is uncertain at present. To draw more definite conclusions requires a larger number of critical experiments.

Nature of Partial Block

The problem of the nature of the partial block which exists in myas-
henia gravis has been studied by various means. The electromyographic
pproach has largely been used with intra-arterial injections of drugs such
s curare, decamethonium and acetylcholine. Only two of the many types
block previously discussed are important in myasthenia gravis: type 3a

—competition block (curare-like), and type 4—depolarization or cholinergic block.

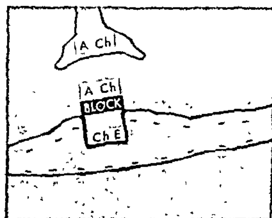


Fig. 26 Schematic drawing showing a comparative block of acetylcholine (Figures 26 through 35 and 41, 42, 44, 49, 56, 57, and 58 are reprinted, by permission, from the film *Myasthenia Gravis*, produced by Sturgis-Grant, Inc., for the Myasthenia Gravis Foundation, Inc., and Hoffmann, La Roche, Inc.)

Many papers have been presented to show similarity between the curare effect and the partial block existing in myasthenia gravis. These similarities have been pointed out in the previous discussion of competitive block. Desmedt[57] dissents from this opinion and states that the neuromuscular block of curare and myasthenia gravis are different. Enduring and reversible increase of neuromuscular block after short periods of intense activity is analogous to the long-lasting component of pathologic fatigue seen clinically. This phenomenon is not seen in the curarized muscle, that is, a simple decrease in endplate sensitivity to acetylcholine cannot account for the entire myasthenic process, not even for its most characteristic clinical features. Post-tetanic exhaustion might result from depletion and deficient resynthesis of preformed acetylcholine in nerve endings, or from an enduring alteration of chemoreceptor mechanisms at the endplate.

Harvey,[58] in studying intra-arterial injections of acetylcholine, suggested that the defect is due either to release of an insufficient amount of acetylcholine or to a blockade at the motor endplate which prevents its stimulation by a normal amount of acetylcholine.

Depolarizing Block Churchill-Davidson and Richardson[59] have studied the effect of decamethonium in high doses in myasthenia gravis. They found that the muscles most affected with myasthenic symptoms are the first to fail and that the clinically normal muscles have a marked tolerance

to the depolarizing action. These data indicate that the endplates of myasthenic muscles have more than normal sensitivity to cholinergic compounds like decamethonium

Foldes[60] has conducted an interesting experiment with the normal human and dog He performs a curare test,[61] using one-twentieth of the normal curarizing dose, and shows that there is no effect of this dose on the respiratory rate and/or volume He then gives decamethonium intravenously slowly over a period of time until complete apnea occurs The anesthetist bag-breathes for the intubated patient until respiration has returned to normal both in volume and rate. A second curare test is then performed and the patient or animal promptly reacts like a myasthenic to this dose and complete apnea occurs. At this point, Prostigmin is injected, with return of respiration to normal, similar to the effect in a myasthenic patient Foldes postulates that perhaps we should be looking for a circulating depolarizing agent rather than a circulating curare-like substance

Competition Block Grob, Johns and Harvey,[62 63] using electromyographic techniques, have published the results of their studies in neuromuscular function These greatly clarify current knowledge of the effect of various drugs in the myasthenic patient They have compared the results in the normal subject with those in the myasthenic The following is a brief summary of their results

In patients with ocular bulbar myasthenia gravis, they showed that there was a reduction in the mean amplitude of the muscle action potential of the clinically uninvolved muscles in response to a single nerve stimulus In patients with general myasthenia gravis, the partial block of transmission at the neuromuscular junction has several characteristic features There is a slight degree of block to the passage of a single impulse Following the passage of the single impulse, there is an increased block to the passage of a second impulse After a train of impulses to the motor nerve, there is first a progressive increase in block to the passage of impulses across the neuromuscular junction This is followed by a transient decrease in block and is later followed by a progressive increase in the degree of block The magnitude of these blocking changes parallels the increase in the stimulating frequency Repetitive nerve stimulation is ollowed after a brief interval by a period of facilitation of neuromuscular ransmission, which represents a decrease in the myasthenic block and probably prejunctional in origin The degree of post-tetanic facilitation ncreased by increasing the frequency or duration of tetanic stimulation ese characteristics of neuromuscular block in myasthenia gravis have ny similarities to the block produced by partial curarization in men l in animals

Pharmacodynamics

Prostigmin (Neostigmine) and Tensilon (Edrophonium Chloride). In patients with myasthenia gravis, intra-arterial injection of Prostigmin or Tensilon produces an increase in the amplitude of muscle action potential evoked by nerve stimulation, followed after larger doses by depression. There is an increase in the reparative and depressant effects of acetylcholine This is compatible with their action mainly as anticholinesterase agents Tensilon has a more rapid onset of action than Prostigmin, suggesting that it may have an additional direct effect on neuromuscular transmission or different diffusibility. D-tubocurarine produces greater depression of evoked potentials in myasthenic patients than in normal subjects and more marked inhibition of the "prompt" depressant (depolarizing) action of acetylcholine. Decurarization by post-tetanic nerve stimulation and acetylcholine is no less striking than in normal subjects. This suggests that the site of the d-tubocurarine in block may be proximal to that of the myasthenic block.

Decamethonium Decamethonium produces a transient increase in the amplitude of evoked muscle potential in myasthenic patients attributable to depolarization followed by progressive depression of successive potentials The initial potential of a train of stimuli is depressed to a lesser degree than in a normal subject, while subsequent potentials are depressed to the same extent The depression has most of the properties of a competitive block, including reversal by acetylcholine, Prostigmin or Tensilon The depression develops more slowly in myasthenics than in normal subjects

Acetylcholine Intra-arterial injections of acetylcholine in patients with myasthenia gravis produce stimulating and depressant effects on neuromuscular function The responses are:

1. A transient stimulation of motor activity attributable to depolarization of motor endplates This was less than in normal subjects, but the difference was barely significant.

2. "Prompt," transient depression of neuromuscular transmission which appears to be due to persistence of the initial depolarization of the endplates This depression is significantly less than in normal subjects, indicating that there is in myasthenic patients a competitive (acetylcholine-inhibitory) block to the depolarizing action of acetylcholine.

3 There is a transient improvement in neuromuscular transmission which does not occur in normal subjects.

4. Finally, there is a "late" depression of neuromuscular transmission which is more marked in the normal subject and again shows the properties of a competitive type of block (progressive depression of successive

potentials in a train of stimuli, inhibition of the depolarizing action of acetylcholine, a reversal of the block by acetylcholine or Prostigmin) This block does not appear to be due to acetylcholine itself. Its time course and resemblance to a comparable degree of block produced by choline suggests that it may be due to choline released as a result of hydrolysis of acetylcholine.

Choline Theory of Neuromuscular Block. Grob et al[62 66] could not clearly define why acetylcholine and choline produced a predominantly competitive type of block in the myasthenic patient and a predominantly noncompetitive block in normal subjects Since decamethonium has similar effects, they postulate that it is likely that the motor endplates of muscles affected by myasthenia gravis may react abnormally to a number of compounds The abnormal response to acetylcholine and choline is of particular importance because these compounds are released during the normal process of motor nerve activity They suggest that this response could be due to an alteration in the endplate or to the formation of an abnormal product of acetylcholine or choline which has complete blocking action Churchill-Davidson and Richardson[67] agree with this concept The longer latent period between the injection of choline and the onset of maximum depression in the myasthenic than in the normal subject, they state, is somewhat more suggestive of the formation of an abnormal product of choline They suggest that a continuing block exists in the resting myasthenic muscle They consider that it is a competitive type of block due to choline liberated as part of the normal neuromuscular transmission process in which choline is released via the breakdown of acetylcholine by acetylcholinesterase (Nachmansohn's theory would explain these observations in terms of failure of the choline-acetylase enzyme system) They present evidence that choline administered intra-arterially can duplicate the myasthenic abnormality in the myasthenic, but not in the normal

There is evidence that acetylcholine is continually released from motor nerve-endings in subliminal concentrations, which may account for the presence of some neuromuscular block prior to nerve stimulation in patients with myasthenia[62 66] The time course and other properties of the "late" depressant effects of acetylcholine suggest that this effect and the neuromuscular block of myasthenia are produced by the choline released following the hydrolysis of acetylcholine Acetylcholine produces three times as much depression as choline per milligram of injectable drug Each milligram of acetylcholine yields only 0 8 milligram of choline on hydrolysis They suggest the possibility that acetylcholine hydrolized in vivo may give rise to choline in closer proximity to the endplates than that which would result from the injection of choline They postulate that

acetylcholine may penetrate more readily into the region of the endplates by reason of its ionic interaction with the receptor protein of the endplate This latter work, if substantiated, would seem to be an important advance in the study of the nature of the defect at the neuromuscular junction of the myasthenic since it postulates a block due to a normally occurring compound at the neuromuscular junction.

Evidence for Nonjunctional Defect

A number of papers inconclusively point to the possibility that the defect in myasthenia may not be specific to the neuromuscular junction. Salmon[68] suggests that the disturbance is one of the autonomic nervous system marked by vagal hypotonia. Lundervold,[69] using electromyographic techniques, concludes that myasthenia gravis may affect normal fatigue mechanisms through other routes than the neuromuscular synapses. Pelikan[70] has pointed out that four per cent of normal subjects are as sensitive to curare as myasthenic individuals. Bergh,[71] in studies of various species of animals, found they reacted differently to Flaxedil, decamethonium, and succinylcholine, probably due to differences in the motor endplate

Papers have been published which draw attention to the muscle itself in contrast to endplate blocking agents. Gammon[47] analyzed Shy's reports of his early studies of sodium and potassium concentration in intra- and extracellular water in human muscle biopsy specimens These have not shown any consistent pattern but have not confirmed Cumming's findings of accumulation of potassium in myasthenic muscles.[47] Glaser[72] reported that the latent period between nerve stimulation and muscle response, and the refractory period of muscle, were prolonged in potassium-deficient animals. At the time of this writing, he is studying the refractory period of muscle in normal subjects and in patients with myasthenia gravis.

Botelho[73,74] in two papers has drawn attention to certain discrepancies between electrical and mechanical activity of skeletal muscles In six patients in whom tension and action potentials were studied simultaneously the changes in tension reflected more accurately the degree of muscle weakness than those changes in the action potential She concludes *that, in some muscles, weakness results from a defect in contractibility* apart from or in addition to a defect in neuromuscular transmission Her claim is that Prostigmin is useful because, in addition to decreasing the neuromuscular block, it can alter the contractibility of muscle. This is not fully supported by the data quoted It would be valuable to have a comparison of normal muscle tension and that in the myasthenic under adequate therapy. This work is now in progress in various laboratories It remains entirely possible that both a major defect in excitability and con-

tractibility of muscle may exist in this disease and that the conflicting statements of Grob and Bohelho can be reconciled by additional techniques of study. Feldman[75] is studying this problem.

Serum Complement

In studying the muscle membrane of the frog muscle immersed in myasthenic serum, which caused appreciable reduction of tetanus tension, it was noted that muscle cell lysis occurred In certain immunologic systems, cell membrane lysis occurs if complement is present From this and additional facts, Nastuk et al[76] decided to investigate the serum complement activity in myasthenic patients Serial complement activities were studied in 45 myasthenic patients and 12 controls. The method used in the study of the serum complement activity was to record the degree of hemolysis created by incubating the serum with previously activated sheep red cells. In this way, a quantitative measurement of the complement could be recorded The complement activity in some myasthenic patients was found to be within the normal range, but in other myasthenic patients the value obtained was far below and sometimes above the extremes of the normal range

In general, the results showed that myasthenic patients in whom the severity of the disease did not change showed a relatively constant complement activity, with values usually lying within the normal control range In patients experiencing remissions and exacerbations, complement activity varied greatly beyond the limits of the control range. There is as yet no evidence which would help to explain the variations in serum complement activity in myasthenia gravis. These experiments suggest that further investigation of myasthenia gravis along immunologic lines may prove to be of value

Endocrines

The possible role of the endocrine system in the pathophysiology of myasthenia gravis will be more fully discussed in the Chapter on Endocrinology It is possible that hormonal principles of the various endocrine glands may have an effect on the enzymatic chemistry involved at the neuromuscular junction in myasthenia gravis At present, some interesting findings point in this direction, but no conclusive results have been established

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CHAPTER IV

Clinical Aspects

SIGNS AND SYMPTOMS

ANY STRIATED MUSCLE group may be affected by myasthenia gravis. Usually the symptoms are multiple, involving more than one group of muscles. The common symptoms in myasthenia are:

Ptosis Ptosis is an involuntary drooping of the upper eyelid which may occur after normal use, may be induced by repeated blinking of the eyelids or by shining a light into the eye. It imparts a sleepy appearance to the patient and can be unilateral or bilateral. To determine the degree of ptosis hold a ruler to the eye to measure the width of the palpebral fissure when the patient looks straight ahead or forcibly opens the eye as wide as possible. This symptom can also be measured by observing the extent to which the upper lid covers the cornea in relation to the pupil. Occasionally the upper lid is so retracted that the eye is kept extremely wide open and the patient is unable to close the eye completely. This is only



Fig 27 Bilateral ptosis



Fig 28 Unilateral ptosis.

seen in the treated case and has been observed in thymectomized patients. This phenomenon is always unilateral, the other lid being ptosed.

Diplopia Diplopia is a morbid condition of vision in which a single object appears double The muscles which turn the eyeball act in pairs, i e., the external rectus of one eye and the internal rectus of the other eye are used in lateral gaze On inspecting the eyes, the two corneas do not appear on the same plane This imbalance can be accentuated by having the patient concentrate on an object held near and at a distance The object is then held at extremes of gaze, both lateral and vertical The rectis lateralis is controlled by the sixth nerve, the superior oblique by the fourth nerve, and all other motions of the eye are innervated by the third cranial nerve.



Fig 29 Diplopia

The *red glass test* is used to determine which muscle and nerve are involved It is performed in the following manner. With the left eye occluded by a hand, the patient is asked to look at a light bulb with the right eye A red glass is then held up to the left eye, and with the right eye occluded, the patient is asked to observe the bulb, which now appears red Then, with the glass remaining over the left eye, the hand is removed from the right eye and the patient is asked to describe the bulb.

The normal individual will state that the white and red bulbs coincide, whereas the patient with diplopia will observe two separate bulbs, one white and one red. The electric bulb is then moved in the six directions of gaze and the nature and amount of diplopia is noted in each field

The data required is: (1) in which direction of gaze there is single vision and in which diplopia, (2) whether the diplopia is horizontal, vertical or mixed; and (3) whether the diplopia increases in any direction of gaze. A rule which is helpful in the interpretation of diplopia is that the image seen by the paralyzed eye always lies on the side toward which the diplopia increases and the diplopia always increases in the field of action of the paralyzed muscle.[1,2]

After paralysis has lasted a long time the symptom of diplopia becomes less characteristic since the image in the paralyzed eye is suppressed and faulty projection is corrected by newly acquired experience. This is particularly seen in children who have myasthenia gravis and have complete ophthalmoplegia without diplopia

Myasthenic Facies The myasthenic facies is a characteristic symptom which is caused by the relaxation of the muscles of the face. The fronto-nasal labial folds are flattened, which renders the features smooth and the expression insipid. The mouth tends to hang a little open. The lips are



Fig 30 Myasthenic facies

full and the underlip is slightly averted The patient has difficulty in smil- [illegible]

[illegible] mouth while the levators expose the canine teeth, resulting in the so-called myasthenic snarl The muscles of the cheek may become relaxed, so that when the patient chews, the food is lodged as a bolus in the cheek Some patients cannot close the lower jaw and therefore tend to support it with the hand

Myasthenic Tongue [illegible]

This is not a particularly important sign

Dysarthria Dysarthria is a characteristic symptom of myasthenia and may take different forms The patient may have a nasal tone due to paresis of the palate The timbre of the voice decreases at times, even to the point of aphonia after continuous speaking Slurred speech may be one of the earliest signs One patient, for example, was presented as a case of conversion hysteria During the course of the history taking by the psychiatrist, the patient's voice became characteristically lower and lower. After referral and work-up, a diagnosis of myasthenia gravis was established

Difficulty in Chewing The patient can bite into food, but as he continues to grind, the power of the masseters decreases until the patient [illegible]

the mouth before and after grinding

Dysphagia The contortions and gyrations of a myasthenic patient with this symptom trying to swallow are an unforgettable sight. Frequently, these patients will have nasal regurgitation of fluids A barium swallow viewed through the fluoroscope will show puddling of the barium in the pyriform sinus [4] If an anticholinesterase drug is administered, the barium will flow quickly past the pyriform sinus and into the stomach

Weakness of the Neck Muscles. At times the muscles of the neck become involved so that the patient cannot hold the head erect and will support his head with his hand. This is often seen in conjunction with weakness of the lower jaw.

Respiratory Weakness Respiratory difficulty is seen in the more serious forms of myasthenia gravis The patient loses the ability to breathe properly and all the signs of air hunger become apparent, particularly



Fig 31 Dysphagia.



Fig 32 Weakness of neck and jaw muscles

tachynea, intercostal breathing, flaring of the nostrils, and cyanosis The changing of posture does not particularly help the myasthenic patient. Only specific drug therapy or the use of a respirator can relieve this serious symptom

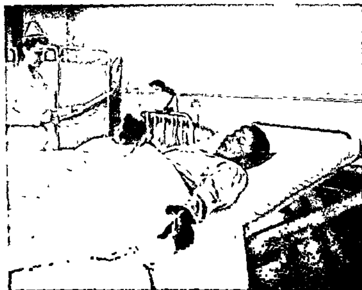


Fig 33 Patient with respiratory weakness in rocking bed

Weakness of the Extremities Weakness of the extremities is a most common symptom in myasthenia Patients may drop objects, may be unable to raise the arms to comb hair, may trip, fall, or may be incapable of stair-climbing Individual muscle groups may be studied in various ways In general, two methods are used The examiner may try to bend the patient's extended arm forcibly while the patient resists to the best of his ability The second method is to have the patient initiate contraction which is resisted by the physician Drift occurs when the patient, with his eyes closed, tries to hold his arms or legs erect for any length of time. Alternate crossing of the legs may become increasingly difficult for the

functions of each group of muscles by repetitive use. When the pelvic musculature is involved, the patient has a characteristic "waddling" gait



Fig 34 Weakness of lower extremities



Fig 35. Weakness of upper extremities

Lower Back Pain. Lower back pain has been identified as a symptom in myasthenia gravis Patients with this symptom have no difficulty in the morning, but the pain develops during the course of the day. Rest or anticholinesterase drugs relieve the pain The orthopedist may be the first to see the patient with lower back pain due to myasthenia gravis[5]

Sensory Changes. Objective sensory changes in myasthenia gravis have not been observed In fact, the older literature states that there are no sensory changes. Harvey[6] was the first to point out that such sensory disturbances as headache, pain in the eye, numbness and tingling of the face, lips, tongue or extremities may precede or accompany the first manifestation of weakness in some cases Fourteen per cent of The Mount Sinai Hospital series had such subjective symptoms at some time in their illness.[7]

Atrophy It was long stated that atrophy does not occur in myasthenia gravis, and when it did appear, it was explained as an atrophy of disuse



Fig 36 Muscle atrophy

after many years of myasthenic disability. As early as 1893, however, Dreschfeld[8] and others[3 9 12] pointed out the presence of muscular wasting Atrophy does occur in a small percentage of patients, particularly atrophy of the quadriceps femoris,[13] and may show up as early as six months after the onset of myasthenia gravis Histologic changes in

biopsied muscle are indistinguishable from those seen in polymyositis or muscular dystrophy [14,16] Confirmatory reports of this dystrophic form of myasthenia have been recorded in the literature.[17,18]

Physical Findings

Usually the myasthenic individual is a well-nourished individu patients plagued with dysphagia are naturally underweight and a to have some form of nutritional deficiency, i e., avitaminosis or an (usually of a microcytic hypochromic nature). The similar muscular w nesses present in myasthenia gravis cause the majority of myasthenic look very much alike

Muscular fibrillation is absent. Tonus of the muscles is not genera altered, although it may be reduced in the severe case. In these cases is not reduced to the degree seen with a lower motor neuron lesion A though the deep tendon reflexes are normal at first, they may be lively o even exaggerated despite a degree of hypotonia being present Continued elicitation of the same reflex, such as the knee jerk, will show a loss of the reflex, which will be recovered after a minute or two of rest. The pupillary reflex is active, but may on rare occasion be sluggish and, like the knee reflex, can be exhausted by persistent stimulation.[19,20,12] Rakonitz [21] in 1929 showed that the myasthenic pupil contracted by light will not become still smaller on accommodation, whereas when contracted by accommodation, it can be further reduced in size by the light reflex

Vasomotor and trophic symptoms are insignificant General physical examination, including blood pressure and heart, gives findings within normal limits, although Wilson [8] has stated that the heart beat may become arrhythmic on exertion

Laboratory Tests

Routine laboratory tests on urine, blood and cerebrospinal fluid are within normal limits A moderate creatinuria with a moderate impairment of creatine tolerance and a slight decrease in creatinine excretion is present in a small percentage of cases [21-24] It has been found only in myasthenics who show muscular atrophy. As a rule, the metabolism of these substances is not significantly altered.

Hellman [25] has studied the 24-hour urine excretion of a few patients and been struck by the variation in the creatinine output from day to day Since the daily creatinine output is supposedly constant in the same patient and is used in laboratories as a means of measuring the 24-hour urine output, he felt at first that the full specimen had not been collected each

day When an indwelling catheter was placed into the bladder and the urine so collected, this variation persisted Furthermore, with paper chromatography he was able to find an unusual creatine spot The significance of this work is not yet apparent.

Other metabolic studies have not been helpful, being ambiguous and contradictory. Increase of lactic acid in the blood and urine has been reported by some workers,[26,27] but denied by others[28-30] Excess of calcium was reported,[31,32] but normal amounts or even a decrease has been seen[33,34] Adams and Power[24] state that calcium, magnesium, sodium, potassium, phosphorus, sugar, urea, creatinine, amino acids and uric acids in the blood are within the limits of health in patients with myasthenia gravis Recent interest in the total proteins and electrophoresis has led to a study of the albumin-globulin ratio and the pattern of the proteins in twelve myasthetic patients in The Mount Sinai Hospital group, without conclusive findings[35,36]

Blood sugars have been reported as normal, hypo- and hyperglycemic.[37,38] Only normal blood sugars in myasthenia gravis were observed in The Mount Sinai Hospital group, with the exception of eight patients who had associated diabetes and three cases of functional hypoglycemia In one of these cases, during performance of a routine, prolonged glucose tolerance test, a typical hypoglycemic episode at four and a half hours triggered a severe myasthenic reaction Fifty per cent glucose alleviated both conditions, whereas Tensilon relieved only the myasthenic symptoms

Incidence of Symptoms

Characteristically, symptoms of myasthenia gravis in the untreated case are mildest in the morning and usually become progressively worse as the day wears on There is always an improvement in symptoms after a period of rest

Kennedy and Moersch,[39] reporting on the symptoms and signs of myasthenia gravis before the days of Prostigmin treatment, found the results in 87 cases that are given in table 1 Table 2 gives the initial symptoms reported by Harvey[6] in 125 cases, while table 3 is based on 60 cases reported by Garland and Clark,[40] who divided symptoms into those present at an early stage and those appearing later. Table 4 is an analysis of 325 cases seen at The Mount Sinai Hospital

Table 4 requires some explanation The high percentage reported in the total reflects the fact that the patients exhibited these symptoms at some time during the course of the myasthenia It does not necessarily mean that all the symptoms were present simultaneously There is usually a multiplicity of symptoms in myasthenia gravis

TABLE I.

Initial Symptoms

Symptoms referring to ocular disturbances	36
Symptoms referring to debility of legs	24
General debility	11
Bulbar debility	9
Facial and mandibular debility	5
Various symptoms	2

Initial Signs

Ocular debility	58
Pharyngeal and bulbar debility	13
Debility of legs	11
Debility of mandibles	5

TABLE 2.

Ptosis, unilateral	28
Ptosis, bilateral	15
Diplopia	35
Weakness of legs	18
Generalized weakness	10
Weakness of hands and forearms	9
Dysarthria	12
Dysphagia	9
Difficulty in mastication	7
Facial weakness	4
Neck and shoulder weakness	2

TABLE 3

	Early	*Later*	*Total*
Diplopia	36	13	49
Ptosis	26	14	40
Asthenia	21	4	25
Arms	12	13	25
Legs	11	12	26
Jaw	6	6	12
Neck	4	3	7
Dysphagia	8	11	19
Dysarthria	11	8	19

TABLE 4*

	Onset (Per cent)		Total (Per cent)	
Ptosis, unilateral	28	57	24	78
bilateral	29		54	
Diplopia	48		70	
Dysarthria	29		56	
Dysphagia	29		60	
Chewing	17		39	
Dyspnea	13		29	
Face	9		36	
Trunk and back	4		20	
Neck	8		29	
Upper extremities,				
unilateral	5	14	12	56
bilateral	9		44	
Lower extremities,				
unilateral	3	15	8	54
bilateral	12		46	
Generalized weakness	24		55	
Subjective sensory changes	Less than 1		14	
Atrophy			6	

*Reprinted, by permission, from Osserman, K E, et al *Arch Int Med*[7]

CLINICAL COURSE

Myasthenia does not have a classical clinical course Usually the muscles innervated by the cranial nerves are the first to be affected, particularly the eyes The onset may be in loss of muscular strength in the limbs In the former type there is a general decrease in muscle strength as more and more of the skeletal muscle groups become involved Finally the [illegible]d to the point

[illegible] ocular myasthenia and the condition remains stable for two years with no further [illegible]

[illegible] the ocular muscles In seven other cases the primary ocular form extended to include other muscle groups at intervals of three to thirteen years after onset

Of the 325 patients in The Mount Sinai Hospital series, 76 had unilat-

eral ptosis, 81 had bilateral ptosis and 133 had diplopia at onset Of this number, 136 had an onset with ocular symptoms only, and in 50 of these patients, ocular involvement remained the only symptom, in 55, there was spread to other muscles occurring within two years after onset, and in 31 the spread occurred late, developing between three and twenty-three years after onset

Spontaneous remission and exacerbation are characteristic of this disorder Some patients improve slowly, while others will change rapidly from a mild to a severe case or the reverse. Other cases remain static. Pregnancy seems to affect the course of myasthenia favorably in about one-third of the cases, while in others it may cause exacerbation

In The Mount Sinai Hospital series, 41 patients or 14 9 per cent showed an exacerbation of symptomatology with upper respiratory infection. Fifty-one of 148 menstruating females, or 34 per cent, showed exacerbation of the myasthenia with the menstrual cycle, particularly in the immediate premenstrual phase These patients improved at any time fr onset to cessation of the menstrual flow

Sex and Age

Schwab and Leland[43] analyzed 367 patients on whom they had accurate information concerning the date of onset of myasthenia gravis The difference in age at onset between male and female was significant: myasthenia developed in 62 per cent of the 202 females before the age of 31, whereas in the 167 males, the onset occurred before the age of 30 in only 27 per cent For the females the mode (21%) onset age was 21 to 25 years, whereas for the males the mode (30%) onset age was 61 years and over

The greater proportion of female over male cases is borne out by Ferguson's series[12] in which 49 of the 75 cases were female. He found that the average age of onset was 34 years and that the range was from the first day of life to 71 years, with maximum incidence in the second, third and fourth decades

Garland and Clark[40] found that their distribution was 35 females and 25 males, but their figures do not corroborate those of Schwab and Leland concerning sex and age at onset Their table shows the male and female incidence occurring almost equally in each decade, and their cases of onset after age 65 years were all female.

Our findings basically agree with those of Schwab and Leland in that there are roughly two females for every male myasthenic. In the juvenile form of myasthenia there is almost an equal incidence in male and female, whereas in the adult form the female develops myasthenia in the early decades of life and the male tends to develop it in the mature decades

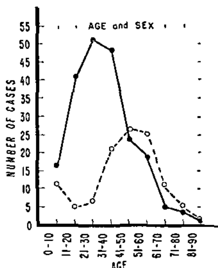


Fig 37 Age and Sex Female 212 (65 per cent, solid line) Male 113 (35 per cent, broken line) Negro 18

Myasthenia may occur from birth to the ninth decade of life In cases of localized myasthenia the male and female incidence is the same. In the other forms the sex incidence varies from two to four females to one male

Clinical Classification

In the course of studying myasthenia gravis, one is impressed with the fact that, like other metabolic disorders, it may not be a single disease but a syndrome composed of many clinical types The following clinical classification, based on many variants such as sex, age of onset, type of onset, localization or spread of symptomatology and prognosis, is helpful in assessing the effects of treatment [43a] (Table 5 subdivides the 325 patients in The Mount Sinai Hospital series according to this classification)

Pediatric

Neonatal This occurs in infants born of myasthenic mothers and is a self-limiting condition usually lasting no more than six weeks The etiologic factor is probably transmission of some substance from the mother to the child across the placenta

Juvenile Unlike the neonatal category, these children are born of nonmyasthenic mothers and tend to have a permanent form of myasthenia This condition may occur at birth or at any time to the age of puberty. There may be

eral ptosis, 81 had bilateral ptosis and 133 had diplopia at onset. Of this number, 136 had an onset with ocular symptoms only, and in 50 of these patients, ocular involvement remained the only symptom, in 55, there was spread to other muscles occurring within two years after onset, and in 31 the spread occurred late, developing between three and twenty-three years after onset

Spontaneous remission and exacerbation are characteristic of this disorder. Some patients improve slowly, while others will change rapid. from a mild to a severe case or the reverse. Other cases remain static Pregnancy seems to affect the course of myasthenia favorably in about one-third of the cases, while in others it may cause exacerbation

In The Mount Sinai Hospital series, 41 patients or 14 9 per cent showed an exacerbation of symptomatology with upper respiratory infection Fifty-one of 148 menstruating females, or 34 per cent, showed exacerbation of the myasthenia with the menstrual cycle, particularly in the immediate premenstrual phase. These patients improved at any time from onset to cessation of the menstrual flow.

Sex and Age

Schwab and Leland [43] analyzed 367 patients on whom they had acc rate information concerning the date of onset of myasthenia gravis Th difference in age at onset between male and female was significant: myas thenia developed in 62 per cent of the 202 females before the age of 31, whereas in the 167 males, the onset occurred before the age of 30 in only 27 per cent For the females the mode (21%) onset age was 21 to 25 years, whereas for the males the mode (30%) onset age was 61 years and over

The greater proportion of female over male cases is borne out by Ferguson's series [42] in which 49 of the 75 cases were female. He found that the average age of onset was 34 years and that the range was from the first day of life to 71 years, with maximum incidence in the second, third and fourth decades

Garland and Clark [40] found that their distribution was 35 females and 25 males, but their figures do not corroborate those of Schwab and Leland concerning sex and age at onset. Their table shows the male and female incidence occurring almost equally in each decade, and their cases of onset after age 65 years were all female.

Our findings basically agree with those of Schwab and Leland in that there are roughly two females for every male myasthenic. In the juvenile form of myasthenia there is almost an equal incidence in male and female, whereas in the adult form the female develops myasthenia in the early decades of life and the male tends to develop it in the mature decades.

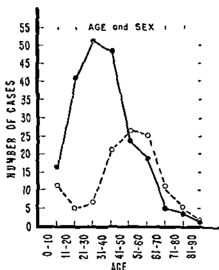


Fig 37 Age and Sex Female 212 (65 per cent, solid line) Male 113 (35 per cent, broken line) Negro 18

Myasthenia may occur from birth to the ninth decade of life. In cases of localized myasthenia the male and female incidence is the same In the other forms the sex incidence varies from two to four females to one male.

Clinical Classification

In the course of studying myasthenia gravis, one is impressed with the fact that, like other metabolic disorders, it may not be a single disease but a syndrome composed of many clinical types The following clinical classification, based on many variants such as sex, age of onset, type of onset, localization or spread of symptomatology and prognosis, is helpful in assessing the effects of treatment [43a] (Table 5 subdivides the 325 patients in The Mount Sinai Hospital series according to this classification)

Pediatric

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Juvenile Unlike the neonatal category, these children are born of nonmyasthenic mothers and tend to have a permanent form of myasthenia This condition may occur at birth or at any time to the age of puberty There may

more than one patient in a family, sisters, brothers and cousins have been reported in this classification. Ophthalmoplegia, complete or partial, with severe bilateral ptosis relatively unrelieved by drug therapy is characteristic.

Adult

Group I A localized, nonprogressive form of myasthenia, with perhaps only one eye affected This may seem severe to the patient, but anticholinesterase [illegible]

has a fairly good prognosis

Group III Acute fulminating onset of generalized myasthenia with severe bulbar manifestations Usually the respiratory system is involved early. In a short time from onset the patient may develop myasthenic crisis These patients do not respond well to drug treatment and have a very poor prognosis

Group IV. Late severe myasthenia which develops usually at least two years [illegible]

lack of use of muscles This group is a descriptive category, and prognosis and mortality statistics depend on the other features shown by these patients.

TABLE 5 *Analysis of 325 Patients*

Group	*Number*	*Percentage*
Neonatal	6	2
Juvenile	28	9
Group I	84	26
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C. Marked clinical improvement with no reduction of anticholinesterase medication
D No clinical improvement, but with reduction in anticholinesterase medication
E. *No change.*
F. Worse
G Dead.

Illustrative Case Histories

Case 1. A white male, 65 years old, with onset of myasthenia gravis in January, 1956, was diagnosed one month prior to his visit to our clinic The only symptom was ptosis of the right eye He was treated with one 15 mg tablet of Prostigmin bromide three times a day with only fair relief of ptosis One week after medication was changed to Mestinon bromide and increased to two 60 mg tablets four times a day, ptosis was completely relieved By May 1956, he was in a remission with no need for medication The remission continues to the present, however, exacerbation may occur at any time This case illustrates a mild type Group I with only a single symptom

Case 2 A white female, 55 years old, a married housewife, with onset of myasthenia gravis at the age of 18 years in 1918 with diplopia Within a year she was in complete remission, which lasted until 1925 She became pregnant for the first time in 1924 and was delivered by low forceps of a normal child She felt very well during this pregnancy In 1925, the myasthenia returned, with dysarthria, dysphagia, difficulty in chewing, nasal regurgitation of food, weakness of both lower extremities and dypsnea During this period the patient was miserable and bedridden most of the time This period was prior to the use of anticholinesterase medication. She became pregnant again at the age of 28 in 1928 and went into a complete remission which lasted until 1953 During this remission she had an induced abortion and developed severe peritonitis without the recurrence of her myasthenic symptoms

In 1953, ptosis returned, with generalized fatigue, particularly involving her lower extremities, and severe low back pain She was treated with Prostigmin bromide, ½ to 1 tablet on an hourly basis, and suffered severe gastrointestinal spasms Medication was changed to Mestinon bromide and she was given two 60 mg. tablets four times a day, with complete relief of symptoms In the past year she has been in and out of remission, with variations in her dose from no medication to two tablets of Mestinon four times a day When in need of medication she has subjective sensory disturbances, i e, pain in her face, neck and arms, which is relieved by anticholinesterase drugs Currently, symptoms have recurred and she requires medication This case illustrates a generalized Group II myasthenia with long periods of remission and exacerbation

Case 3 A white female, age 19 years, a student, was essentially well until the age of 17 years, at which time, in September 1954, she developed episodes of drooping eyes From September to December she had several episodes of ptosis, diplopia, slurred voice, and difficulty in swallowing In December, a Tensilon test was positive and she was hospitalized. A work-

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Group I A localized, nonprogressive form of myasthenia, with perhaps only one eye affected. This may seem severe to the patient, but anticholinesterase drug therapy corrects the defect in the greater majority of patients Occasional patients are resistant to drug therapy. This group has an excellent prognosis

Group II. [illegible]
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remain static [illegible]
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Group V [illegible]

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Group II Generalized myasthenia involving more than one group of striated muscles, both bulbar and skeletal, with gradual onset. This moderate form may remain static for long periods of time. Spontaneous remission or exacerbation may occur early or late This group is usually amenable to drug treatment and has a fairly good prognosis

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up was essentially negative, including chest films The patient was
with 1½ tablet Prostigmin bromide with atropine three times a d
was discharged with partial relief.

From December 1954, to February 1955, the patient continued t
the same complaints. She lost weight, dropping from 130 to 117 p
Despite increased dosage of Prostigmin she became increasingly
The patient was referred to us in February 1955, at which time sh
placed on 2½ tablets (150 mg) Mestinon bromide every two and
hours Although this proved somewhat more effective than Prostigm
continued to have severe symptoms.

On March 4, 1955, we wrote her physician: "We are a bit conc
about your patient because of the severity of her bulbar onset. Thi
of case tends to go into crisis rather quickly. She should be continu
Mestinon therapy and watched carefully for the next few months.
does not show decided clinical improvement, this is the type of c
which thymectomy might be of value"

On May 2, the patient was admitted to The Mount Sinai Hospit
thymectomy. Diagnostic work-up was essentially negative. Posterior
rior and lateral chest films showed no enlargement of the thymus g
The patient was maintained for several days on 2½ to 3 tablets (1
180 mg) Mestinon bromide every two and a half hours She did not
to respond adequately, so, after an intravenous titration, her dose
raised to 5 tablets (300 mg) Mestinon every two and a half hours. W
awaiting thymectomy the patient developed severe myasthenic respir
weakness and required as much as 17 to 18 mg Mestinon bromide i
venously to maintain respiration This is equivalent to 9 tablets (540
every two hours Because of the high dosage and the resistance to me
tion, it was decided to place the patient in a respirator and witho
medication After two days in the respirator the patient improved.
patient was removed from the respirator, therapy with Mestinon
reinstituted, and she improved to about admission level status. On
sixteenth hospital day a thymectomy was performed by the sternal s
ting technique and a bilobe, normal appearing thymus was removed
pathologic report showed no histologic abnormality.

The patient was maintained on intramuscular Mestinon bromide p
operatively. She ran a temperature to 102° and breathed and coug
poorly On the second postoperative day, it was noted that in additio
general impairment of breathing, she was cyanotic despite contin
oxygen therapy No breath sounds were heard in the left lung Bed
bronchoscopy was performed and the left main bronchus was cleare
thick secretions She had another episode of cyanosis and a tracheosto
was performed, with considerable improvement.

Postoperatively, there was a decrease in Mestinon requirement, both in amount and frequency, and she displayed increasing strength The tracheostomy tube was removed one week later By the third postoperative week, the patient was markedly improved Medication was Mestinon, 4 tablets (240 mg) three times a day The ptosis and diplopia had all but [illegible]

[illegible] had an upper respiratory infection with marked increase in symptoms, particularly difficulty in swallowing

She ran a static course with not much change in symptoms until March 1956, at which time her engagement to be married was broken With this emotional trauma her myasthenic symptoms became worse Mytelase was substituted for Mestinon in an attempt to halt her downward course Mytelase was ineffective and was discontinued in May She was readmitted to the hospital in June 1956, because of progressive weakness, *inability to swallow and slight respiratory distress without cyanosis for* the preceding four days Her weight was now down to 82 pounds The [illegible]

[illegible] tion, there was no true relief In fact, the dose had to be lowered gradually to avoid cholinergic responses The patient became so sensitive to medication that ⅛ of a tablet (7½ mg) was too much and created difficulty She was discharged in a fair condition

She was readmitted to the hospital for the third time in October 1956, and had to be placed in a respirator for 24 hours No tracheostomy was performed, but anticholinesterase medication was withdrawn Currently, with a dose of only ¾ tablet (45 mg) Mestinon every two and a half to three hours, the maximum she can take, the patient has a severe form of myasthenia, with little of her symptomatology relieved Her mother must nurse her practically all hours of the day, the patient being unable to fend for herself

Thymectomy may have prolonged this patient's life in view of the fulminating type of pattern she had been running This case illustrates a severe form of Group III type of myasthenia gravis.

Case 4 A white female, 58 years old and a married housewife, at the age of 34 in 1934 experienced weakness of both upper extremities, the fingers of the right hand being particularly involved Within a few months bulbar symptoms developed in the form of ptosis, myasthenic face, inability to smile or hold her chin up In addition, dysarthria became evident.

There was no difficulty with swallowing or respiration. For the next year she continued in this manner, undiagnosed and untreated. In 1935, following a minor operation, the patient went into a complete remission which lasted for two years. Symptoms then recurred, and in 1937 the patient was diagnosed as having myasthenia gravis. Administration of Prostigmin intramuscularly was instituted, and she was subsequently treated with one tablet of Prostigmin three times a day On this regime her symptoms were easily controlled Her conditions remained static until 1954, at which time there was need to increase the dosage of Prostigmin to one and one half tablets every three hours In 1955, she was transferred to Mestinon bromide, approximately one tablet every two hours, which she found to be very efficient. From time to time she has taken ephedrine as an adjunctive therapy When first seen at The Mount Sinai Hospital in 1956, the patient displayed no symptoms while on medication Medication was withdrawn for a period of twelve hours and only facial weakness and ptosis were clinically discernible. The hand grips as shown both by dynamometer and ergogram readings revealed no serious weakness. The patient's Mestinon medication was adjusted to one and one-half tablets of Mestinon three times a day During the next year, the dosage of Mestinon was gradually decreased to three-quarters of a tablet per dose. From December 1956, to October 1957, the patient was not seen, for, as she stated, she was well enough not to require observation. Early in October she began to be troubled with respiratory distress and had a severe recurrence of marked generalized weakness involving all limbs, with return of ptosis, dysarthria, weak neck muscles, inability to smile, to chew and to swallow The patient was admitted to the hospital Attempts were made to adjust medication, without any real relief of clinical symptoms X-ray examination, including lateral tomography, showed a small mass, thymoma, in the anterior mediastinum above the cardiac shadow A course of cobalt$_{60}$ teletherapy was given in the amount of 6,000 r directed to the thymus in the anterior mediastinum By mid-December 1957, there was a slight clinical improvement and her dosage of Mestinon was decreased to one half tablet every two to two and one half hours This case illustrates a late severe spread in a former Group II myasthenic who apparently developed exacerbation in association with the formation of a thymoma

Case 5 A 49 year old, white female, married housewife, had an onset of myasthenia at the age of 48 years, with ptosis, dysarthria, dysphonia, and difficulty in chewing She was treated with 1¾ tablet (27 mg) Prostigmin for a period of six months with fair effect She was first seen by us in January 1956, six months after the onset of myasthenic symptoms, at which time all the presenting symptoms were apparent plus weakness of

the face, neck, trunk, back and lower extremities, with atrophy of both quadriceps She had difficulty rising from a chair and walked with a typical "waddling" gait She had had her menopause two years prior to the onset of her symptomatology.

An attempt to improve the status of the patient was made by changing her drug to Mytelase, which she did not like Mestinon bromide was then tried, 3 tablets (180 mg) every three hours, for a period of two months, with only a poor effect She was hospitalized so that an attempt could be made to achieve better control In the course of diagnostic work-up, no abnormalities other than the myasthenic symptoms were found There was no enlargement of the thymus Radiotherapy in a dose of 2000 r was given to the thymic region.

Mestinon dosage was gradually increased to 6 tablets At this level there was a fair response in that her bulbar symptoms were improved but there was little effect on her ability to walk Prolonged action tablets of Mestinon bromide were prescribed (6 tablets three times a day), which gave the patient best relief Currently, her bulbar symptoms are controlled and the patient can walk about the house sufficiently to take care of her personal needs She is, however, still a severe myasthenic, requiring attention from her family No change in the atrophy of the quadriceps has been noted This case illustrates the dystrophic Group V form of myasthenia gravis

Case 6 A 51 year old, white widow noticed the onset of diplopia in 1953 At first, this was present only when looking to the extreme of lateral gaze She next developed pain and stiffness of the neck There was a remission of symptoms for the next few months, until she again noted diplopia of the horizontal type of distant vision She was given a Prostigmin test, which made the diplopia worse Another remission occurred which lasted until November 1955, at which time diplopia returned and became progressively worse Double vision vertically and horizontally was constant

She was admitted to a hospital, and a complete work-up, including electroencephalography, spinal tap and complete neurologic survey, gave normal findings except for the diplopia. When first seen by us in October 1956, the only symptoms displayed were diplopia and ptosis of the right upper lid which was made worse both by the shining-light test and exercise A Tensilon test relieved the ptosis but had no effect on the diplopia.

She was given a therapeutic trial of Mestinon, ¾ tablet (45 mg) three times a day, and reported two weeks later that she felt much better The diplopia was not changed, but the ptosis was completely relieved With the patient in a basal state, a red glass test was performed before and

after 2 and 5 mg. of Tensilon The diplopia became worse but the ptosis was relieved

When medication fails to clear all presenting symptoms, the diagnosis of myasthenia is frequently withheld, as was done in this case for two and a half years. This is distressing and confusing to the patient and the physician A false-negative response is more prone to occur with the rigid dose schedule of the Prostigmin test than with the Tensilon test.

This Group I patient illustrates the lack of response of one muscle group to anticholinesterase medication. In fact, her diplopia was increased when Prostigmin or Tensilon was administered.

Incidence of Myasthenia Gravis

Cases of myasthenia gravis have been reported from all over the world, but the incidence of this condition has not been accurately determined at the present time and estimates vary radically. At one time, Viets[44] postulated that there were only 2,000 cases in the United States. This low figure is supported by Garland and Clark[40] who, on the basis of a personal study of 60 cases in an English city, estimated a ratio of one case in 40,000 population and therefore assumed that there would be 2,000 cases in all of Great Britain. If we apply this ratio to the United States, we would arrive at a figure of 4,250 cases. Eaton,[45] on the basis of his personal experience in Rochester, Minnesota, places the incidence at one in 15,000 to 20,000. He arrives at the figure of 10,000 known myasthenics in the United States and believes that there are one or two undiagnosed cases for every known myasthenic, which would raise his estimate to 30,000 Tether[46] estimated that there was one case in 3,000 population in the United States.

Kurland[47] has presented data based on reported death rates from several countries and morbidity statistics in two small communities. He states that this data provides minimal rates which can serve as a reasonable point of departure for further statistical study. In Charleston County, South Carolina, a study of his still in progress indicates that the diagnosis of myasthenia was made in twelve patients in the past ten years As of December 31, 1955, nine of these patients were still alive *The 95 per cent* confidence limit is 3 5 to 15 8 cases for the community and the rate varies between 18 and 84 cases per million population

The mortality statistics from Norway and New Zealand, which give a death rate of one per million per year, depend upon too small a population and too low a mortality rate to be truly significant. For Canada and the United States, which offer larger samples, Kurland's mortality statistics indicate a death rate due to myasthenia gravis of 2.4 per million

population per year He assumes an average duration of the disease of twenty years in estimating the minimum prevalence of living patients Ganado[48] reports that Malta, with a population of 300,000, has one new case about every two years Kurland concludes that there is no indication from the limited data that there is any appreciable difference in incidence in the United States by race or geographic location, and only a slightly greater incidence in the female than male His reasonable estimate of prevalence is about 50 per million, or for the present United States population about 8500 affected persons

One must remember that many cases of myasthenia escape diagnosis. As an analogy, it has been estimated that there are 1,000,000 known cases of diabetes in this country and another 1,000,000 undetected cases, which is perhaps a conservative estimate In diabetes it is largely the mild diabetic who escapes detection, since, because of wide recognition of the disease and the ease and frequency of performing sugar detection in urinalysis, any patient complaining of diabetic symptoms is usually quickly diagnosed In myasthenia it is not only the mild myasthenic but also the severe cases which may escape detection One could say that for every known myasthenic, at least two cases are undetected One of my residents started a practice in a small suburb and discovered five cases of myasthenia in two years

It must be cautioned that all cases of fatigue, ptosis or diplopia are not myasthenia by any means As pointed out by Viets and Schwab,[50] only one out of three cases referred to them as possible myasthenics have myasthenia This ratio is very close to that reported from my group[51]

Needham[52] of the Statistical Study Department of Eli Lilly & Company

Foreign Commerce (House of Representatives) during a hearing conducted on "The Causes, Control and Remedies of the Diseases of Mankind" would be the most accurate estimate Further studies, particularly of the Kurland type, will eventually establish the true incidence of myasthenia gravis

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CHAPTER V

Diagnosis

THE DIAGNOSIS of myasthenia gravis in the patient who demonstrates the classical signs and symptoms is comparatively simple, but the very early case or one in which there are equivocal symptoms may defy the diagnostic acumen of the physician.[1]

A high degree of suspicion of myasthenia is always a most important factor in its diagnosis. When a history is taken, the proper questions can then be asked, with special reference to the onset of weakness and its relationship to time of day and effort. The patient usually feels stronger on awakening and becomes progressively weaker by late afternoon or evening. Occasionally, the severe myasthenic under treatment may state that his worst hours are upon arising. A history of increased symptoms with exercise and improvement after rest is typical. It should be determined whether there have been episodes of ptosis, diplopia, nystagmus, dysarthria, difficulty in chewing, nasal regurgitation of food, dysphagia, dyspnea, or weakness of skeletal muscle groups.

The date of onset of the first symptoms and the anatomic site should be noted.[2] It is important to determine whether the symptomatology has remained static, regressed or progressed.[3] A history of remission is probable since early in the onset there may be periods of complete freedom from any symptomatology. In the menstruating female,[4] it is important to determine what influence the period has on the symptomatology. Frequently, the patient will state that symptoms become worse just prior to the onset of the period and improve in the first and second day. Thirty-four per cent of menstruating patients gave such a history in The Mount Sinai Hospital series.[5]

Pregnancy is another vital part of the history in women. Did the symptoms change or begin during a pregnancy? It was found that about one-third of the patients had the onset or an exacerbation of symptomatology during pregnancy or the postpartum period. Another one-third experienced marked improvement or even remission during pregnancy.[6]

As will be discussed in a later chapter, myasthenic mothers may deliver children who have a transient neonatal form of myasthenia.[7,8] It is important to determine what happened to the children born of mothers in whom a diagnosis of myasthenia gravis is being considered. Were they born weak? Was there a neonatal death attributed to intracranial injury or

asphyxia? Such a history would point to a possible diagnosis of myasthenia gravis in the mother

Other factors which should be investigated since they influence the course of myasthenia gravis are infections and emotional trauma Frequently, when infection occurs, such as in the upper respiratory tract, myasthenic symptoms are aggravated Upsetting incidents in school, family or at business may aggravate the symptomatology Cases have gone into myasthenic crisis following severe difficulty in the family life For instance, Meyer[9] describes a patient who received a telegram telling of her son's death and fell to the floor immediately after reading it. This was not just a faint, but the onset of myasthenia gravis This type of onset is most unusual, however, generally, there are prodromal weaknesses for some time before the evident symptomatology appears

In occasional cases, sensory disturbances may precede or accompany the first manifestations of weakness[10]

The question has frequently been asked whether myasthenia can affect only one muscle group This has been seen and reported in monocular *ptosis by many observers*[11,17] *Dysphagia*[18] *and dysphonia has also been* seen as the sole symptom of myasthenia An unusual complaint is "stopped-up" ears with diminished hearing due to relaxation of the muscles that keep the eustachian tube open in the nasal pharynx. In one case the only presenting symptom was a paresis of the muscles of the soft palate

Family history is almost always noncontributory since myasthenia gravis is not an hereditary disease There are reports of some familial incidence in cases of juvenile myasthenia[19] In one instance, attending physicians were loathe to accept the diagnosis of myasthenia gravis in a middle aged woman with bilateral complete ophthalmoplegia and ptosis whose sister was similarly afflicted Investigation of the literature revealed, however, that this patient and her sister had been reported as myasthenics some thirteen years previously by Riley and Frocht[19]

ten holes of golf, baseball, or even, as in one case, work as stevedore.

Physical Examination

Physical examination must be complete and thorough It should be performed when the patient is demonstrating the severest form of his symptomatology, therefore, if the patient is taking any anticholinesterase medication, he should be seen in a basal state, i e, drug treatment should

be stopped for as long a period prior to examination as is compatible with the patient's ability to come to the office This period varies from patient to patient. The milder case may be able to stop medication the night before he is seen Others may only be able to skip one dose or may have to continue regular medication, *arriving for examination at the approximate* time the next dose is due.

After a medical check-up, a neurologic examination is performed, testing for cranial nerves, for deep and superficial reflexes and abnormal reflexes Muscle function is tested most carefully, noting strength, tonicity, spontaneous fasciculations and atrophy.

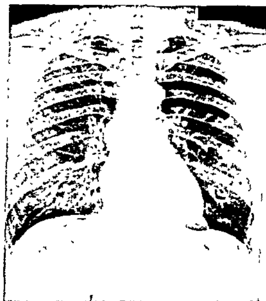


Fig 38 X-ray, P-A, showing thymoma

The width of the palpebral fissure at rest, the maximum fissure with the eye in upward gaze, the excursion of the ocular movements, the power of the masseters, and the strength of the limbs are measured. All of the more important skeletal muscle groups are tested, with special attention to slight asymmetries in muscle power The fatigability of muscles is tested by re-evaluation of strength after repeated use of the muscle, as in blinking the eyes, chewing, exhausting the voice by counting numbers, by walking steps, deep knee bends and rhythmic alternating movement of the limbs Whatever muscular movement is tested, there must be a re-

turn of power, at least in part, in all cases of myasthenia gravis after a period of rest.

Routine laboratory studies such as urinalysis and complete blood count are done. A routine chest film in posterior-anterior and lateral views is necessary to establish the status of the thymus gland. Fluoroscopy, using the oblique positions, is very helpful. If the status of the thymus is doubtful after these procedures, lateral tomograms are ordered. Routine electrocardiography is recorded, but generally is not significant in the younger group of myasthenics. Other laboratory procedures are performed as indicated by the history and physical examination. Postprandial blood sugar and even glucose tolerance tests may be necessary to rule out diabetic neuropathy. Basal metabolic rates, protein-bound iodine and radioactive iodine uptake (I_{131}) should be determined to rule out thyroid dysfunction. Occasionally, x-rays of the sella turcica are required. Blood chemistries, such as studies of the serum electrolytes, may be helpful in ruling out periodic familial paralysis. Routine spinal taps are not required as the results are negative in myasthenia.



Fig. 39. X-ray, lateral view, showing thymoma



Fig. 40. Lateral tomogram showing details of thymoma

Upon examination the myasthenic patient will have normal physical signs, including normal reflexes, no objective sensory changes and no fasciculations. Increased fatigability of muscle groups upon repetitive use

is the most important positive physical diagnostic feature. Evidence of thymic hyperplasia or thymoma is highly suggestive of myasthenia gravis.

Pharmacologic Tests

The diagnosis of myasthenia gravis is established by the administration of drugs which, in proper dosages, affect the myasthenic muscle but have no effect on the normal muscle.[20] There are two groups of drugs used in making the diagnosis: (1) those which stimulate the neuromuscular junction, thereby increasing the strength of the muscle tested; (2) those which inhibit the neuromuscular junction, thereby causing weakness in the muscle tested.

Stimulating Drugs

Drugs which stimulate the neuromuscular junction are the best diagnostic test A placebo test with water, atropine or nicotinic acid may be performed prior to testing with any anticholinesterase drug to aid in interpretation and to rule out false-positive responses in the suggestable patient The examiner must look for objective evidence of improvement and not depend on subjective responses

Prostigmin Test (Neostigmine) With the introduction of Prostigmin, administration of this drug became the basic procedure in diagnosis[21] It may be given in one of three ways intramuscular injection of 1 5 mg of Prostigmin methylsulfate alone or combined with 0 6 mg. of atropine [illegible] intravenously,[22]

[illegible] stigmin

[illegible] scored

tablets for oral administration, Prostigmin methylsulfate for parenteral administration in 1 ml ampules of 1-400 dilution, 0.25 mg per ml, 1 ml. ampules and 10 ml vials of 1-2000 dilution, 0 5 mg per ml; or 10 ml vials of 1-1000 dilution, 1 mg per ml The commonest means of testing with Prostigmin is the intramuscular method The patient is given an injection of Prostigmin methylsulfate and re-examined at five and ten minute intervals for a period of 40 to 50 minutes, both subjective and objective improvement, or lack of it, being noted.

The same observations are carried out for the intravenous test; however, the response starts within one or two minutes *False-negative results* with this test may occur because of the amount of dosage used The patient may be sensitive to Prostigmin and with 1 5 mg. or 1 mg intramuscularly or 0 5 mg given intravenously, the weakness of the disease may be replaced by weakness of over-depolarization. The intravenous Prostigmin test cannot be repeated with increasing doses at the same visit In the event the intramuscular test is equivocal after 1.5 mg. has been given, and

in the absence of side-reactions, the test may be repeated using 2 5 to 3 mg at a subsequent visit If the result of either test is equivocal, the patient may be given a therapeutic trial with Prostigmin bromide orally, usually one to two 15 mg. tablets three times daily The patient is observed for one week for subjective and objective improvement

Tensilon Test (Edrophonium chloride). About 1949, certain phenolic quaternary ammonium salts began to be studied for their effect on neuromuscular junction One of these, Tensilon chloride (3-hydroxy phenyldimethylethyl ammonium chloride), received particular attention[23] It is an analogue of Prostigmin and has a marked anticurare action It was thought to work directly on the neuromuscular junction without any, or minimal, anticholinesterase effect[24 25] At our laboratory, a 15 to 20 per cent inhibiting action on the true red-cell cholinesterase in vivo was found. Nastuk has shown that Tensilon chloride is a true anticholinesterase[26]

It is interesting to note that in the years 1950 and 1951, this drug was tried as a treatment drug in many centers[27,28] Because of its short duration of action, its use was discontinued although it was effective in relieving symptoms of myasthenia Its very disadvantage as a treatment drug, namely, its brief effect, made it an excellent testing agent for this disorder. Our results with fifty patients tested with Tensilon were reported in



Fig 41 Before Tensilon test Patient showing ptosis.

Fig 42 30 seconds after Tensilon test. Ptosis relieved.

1952.[1] We concluded our report with the recommendation that Tensilon chloride be employed as a rapid diagnostic test for myasthenia gravis, since the total testing time often amounts to less than two minutes

In the following three years the Tensilon test was used as a diagnostic procedure in over 300 patients referred to our clinic as possibly having myasthenia.[29] The diagnosis of myasthenia gravis was established in 110 of these patients On the basis of experience in performing thousands of Tensilon tests both for diagnosis and management, certain refinements of the test were recommended.[30,31,32]

In the normal subject, administration of Tensilon causes no change in muscle strength Cholinergic side-reactions such as sweating, salavation, lacrimation and epigastric distress may occur, and fasciculations are almost always noted. (Fasciculations are rarely if ever present when Prostigmin is used as a testing agent) The diagnosis of myasthenia gravis with the Tensilon test is not dependent upon the presence or absence of fasciculation alone. It is important to emphasize that positive responses (marked improvement with minimal side-reactions) to Tensilon usually occur in the myasthenic within the first minute of the injection The effects of Tensilon are usually over within five minutes and the patient with myasthenia gravis then returns to pretesting status.

Current Diagnostic Tensilon Test. Tensilon chloride is available as a 10 ml vial containing 10 mg. of the drug per ml A tuberculin syringe containing 1 ml (10 mg.) of Tensilon is prepared with an intravenous needle, 0.2 ml (2 mg) of Tensilon is injected intravenously within 15 seconds and the needle left in site. Only if no reaction occurs after 30 seconds is the remaining 0 8 ml. of Tensilon injected. If a cholinergic reaction occurs after the injection of 0 2 ml, the test is discontinued and atropine sulfate 1 mg. is administered, after one-half hour the test is repeated with 0 05 and 0.1 ml. (0 5-1 0 mg) of Tensilon

Dosage for children The intravenous testing dose of Tensilon in children weighing up to 75 pounds (34 Kg.) is 0 1 ml (1 mg) For children above this weight, the dose is 0 2 ml. (2 mg). *Because the intravenous* route may be difficult in children, an intramuscular route may be used In children weighing up to 75 pounds, 0 2 ml (2 mg) of Tensilon is injected intramuscularly. In children weighing more than 75 pounds, 0 5 ml. (5 mg) *is injected intramuscularly.*

Intramuscular test in adults In adults with inaccessible veins, the dose for intramuscular injection is 1 0 ml. (10 mg) of Tensilon In subjects [illegible] the test is repeated with

eac-

pear

with the intramuscular test, except that there is a delay of two to ten

minutes before reaction takes place Unlike Prostigmin testing in which the effects last for an hour or two, the reaction to Tensilon wears off within a period of five to ten minutes

Although both the Prostigmin and Tensilon tests are excellent, the Tensilon test is superior in some respects (1) the rapidity of the examination; (2) improvement of the patient occurs so fast that the examiner

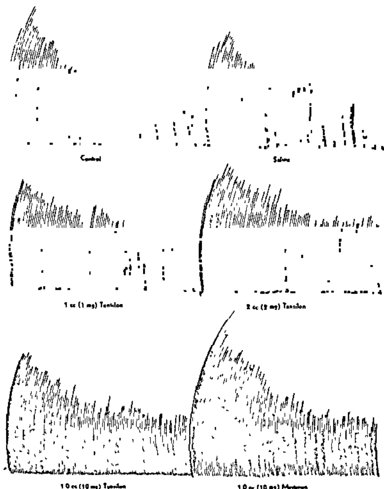


Fig 43 Serial ergography showing response to injection of increments of Tensilon chloride (Reprinted, by permission, from Osserman, K. E., and Teng, P., J.A.M.A. 160 153 1956

can determine relatively minor degrees of change; (3) additional information is available through the presence or absence of fasciculations, (4) in case of doubt, the test may be repeated at the same visit. For more leisurely examination, the Prostigmin test permits observation of improvement lasting for at least an hour. Many examiners combine both tests, starting first with Tensilon and confirming results with an injection of Prostigmin. This is unnecessary as all information required is obtainable from the Tensilon test. Whenever these drugs are used for testing, a syringe containing 1 mg of atropine sulfate (2.5 ml. of 1/600 gr. atropine per ml.) should be immediately available to counteract the severe cholinergic responses which may occur in the hypersensitive individual, be he normal or myasthenic. In patients prone to syncope upon being injected, the tests should be performed with the patient lying down.

A false-negative response to Tensilon, Prostigmin or any anticholinesterase agent employed for the purpose of testing may be explained by the pathologic physiology of the disease and the pharmacodynamics of these drugs. The patient is rapidly brought from a myasthenic state into a cholinergic response. This can be explained on the basis of drug dosage. After clinical trial, 0.2 ml. (2 mg.) of Tensilon was selected as a testing dose for myasthenia gravis when a cholinergic response was elicited with 1 ml. (10 mg.)[30,33] Subsequently, graded doses were evaluated.[29] With 0.2 ml. (2 mg.) of Tensilon there was only a moderate improvement over the 0.1 ml. test. A plateau was reached at 0.2 ml. (2 mg.), with only slight improvements to 1 ml. (10 mg.). Patients who are hyper-reactive to Tensilon demonstrate their best results with 0.1 ml. (1 mg.), whereas with 1 ml. (10 mg.) they show weakness from overdosage. Some subjects recorded improvement in grip strength with the administration of 0.1 ml. (1 mg.) of Tensilon, however, conditions such as ptosis or diplopia were not always completely relieved until 0.2 ml. (2 mg.) or 0.4 ml. (4 mg.) or even 1 ml. (10 mg.) was given.

Tether[22] and Eaton[34] have both advocated Tensilon used in increments for testing in diagnosis, a method first devised by us.[29] More information is obtained by this method than by using arbitrary doses. In the majority of cases, however, the method described above gives all the information necessary and simplifies the test.

Oral Mestinon Test. Tether[35] has advocated an oral test using Mestinon bromide because of its decreased side-reactions. The patient is started on 15 mg. (¼ tablet) three times a day after eating. Every two days the individual dose is increased 15 mg. until a dose of 120 mg. (2 tablets) three times a day is reached. If at any time muscarinic reaction occurs, there is no further increase in dose level. When side reactions intervene, 0.6 (1/100 gr.) atropine orally is taken by the patient every 15 minutes until

the reactions are controlled or a dry mouth develops In cases of severe reaction, the dose of atropine is doubled If no improvement in asthenia occurs before side-reactions arise, it is unlikely that the patient has myasthenia If neither improvement in weakness nor side-reactions develop at a two tablet level, the dose of Mestinon is increased until one or the other intervenes Tether states that improvement is only presumptive evidence of myasthenia and that the diagnosis must be confirmed by an intravenous test.

Inhibiting Drug Tests

There is a group of drugs, quinine[36] *and curare,*[37] *which have a definite* deleterious effect on the myasthenic subject who is hypersensitive to their action In the equivocal case the use of these drugs, with suitable safeguards to prevent psychic effects, will result in increasing weakness in the myasthenic patient These drugs as a group are falling into disrepute as diagnostic agents because of their potentially dangerous effect on the myasthenic subject Their usefulness is confined to those cases in which the diagnosis is seriously in doubt

Quinine Test All anticholinesterase medication is withdrawn for at least 24 hours If the patient then does not exhibit typical myasthenic symptoms, quinine in doses of 0 65 grams (10 grains) is given every two hours. The drug is stopped as soon as myasthenic symptoms intervene or three doses have been given The use of quinine is dangerous because it is a nonreversible type of test, it should never be used in patients with weak cough or respiratory difficulty

Curare Test There are 3 mg of d-tubocurarine per ml in the stock vial The curarizing dose for normal individuals is 3 mg per 40 pounds of body weight The patient to be tested is weighed and one-fifth of the normal curarizing dose is estimated This amount is drawn into a 10 ml syringe and is then diluted to the 10 ml. mark with saline Of this diluted curare, 2 5 ml contains one-twentieth of the normal curarizing dose In cases in which there is clinical suspicion of myasthenia, only 1 ml is given intravenously In other cases not clinically suspect, the first dose may be 2.5 ml The patient should be observed 3 to 5 minutes for appearance of weakness (myasthenic symptoms) If no weakness has developed, a $1/10$ dose (5 ml) may then be injected intravenously At all times a syringe with 10 mg Tensilon (1 ml) and another containing 1 5 mg Prostigmin must be available to counteract any induced severe myasthenic symptoms Artificial respiration and even use of a respirator may be temporarily required to overcome apnea This test should never be used if the patient exhibits any clinical evidence of myasthenia, particularly in those who have had any respiratory embarrassment Its value is in doubtful cases

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exhibiting weakness of muscles commonly involved in myasthenia gravis but who present no objective evidence of the disorder.

The test is presumed to be positive if myasthenic symptoms develop at any dose level up to one-twentieth of the normal curarizing dose. At the one-tenth level, very slight ptosis may develop in the nonmyasthenic, or profoundly weakened muscles, the result of some other disease, may become perceptibly weaker.[20]

Tether,[28] by use of the curare test with a subsequent intravenous injection of Tensilon or Prostigmin, has diagnosed many cases of myasthenia. However, in two of our patients who received only one-twentieth of the normal curarizing dose intravenously, a respirator was required due to the paralyzing effect of the curare on the respiratory muscles, which were not clinically suspected to be affected.

As an interesting sidelight, a case may be cited of a female in her twenties who had such bizarre and varying symptoms that half the physicians who saw her believed that she did have myasthenia and the other half were equally certain that she did not A curare test was performed and startling weakness developed after the injection. The following day the patient was tested with saline instead of curare and even more dramatic weakness developed.

In addition to the pharmocologic tests, many aids have been employed to confirm the diagnosis of myasthenia. These include biochemical assays and mechanical and electrical measurements. These are used in combination with the drug tests.

Biochemical Tests

These tests, particularly of cholinesterase activity[38] both true and pseudo, and acetylcholine levels,[39] have been suggested as possible diagnostic tests for myasthenia gravis Torda and Wolff[40] have conducted biochemical tests in invitro studies which indicate deficiency of acetylcholine synthesis in the presence of serum or spinal fluid from myasthenic subjects Boshes[41] in a preliminary report has found increased cholinesterase enzyme in the cerebrospinal fluid In our laboratory, studies in cholinesterase and acetylcholine blood levels in vivo do not seem to show a statistical difference between the normal controls and myasthenic patients

Mechanical Tests

The Dynamometer and Ergogram

A quantitative measurement of the exhaustion of neuromuscular function is achieved with use of the hand *dynamometer or ergograph*[42] which

measures strength of muscle grip With the hand dynamometer, ten consecutive readings are taken, alternating between the right and the left hand, to see if there is a degradation in the pressure of either hand

Degradation of muscle grip can be graphically shown with the ergograph A bulb ergogram requires 105 grips of the bulb to perform a test. A bell rings each second as a signal for contraction. The normal person will show only a late gradual decrease in ability to press the bulb, whereas the myasthenic will show a rather quick fall-off and may even reach zero long before the 105 seconds are over. In performing serial ergographs, a five minute rest between tests is sufficient to overcome fatigue Even in patients who do not complain of upper extremity symptoms the ergograph recordings may indicate myasthenic weakness

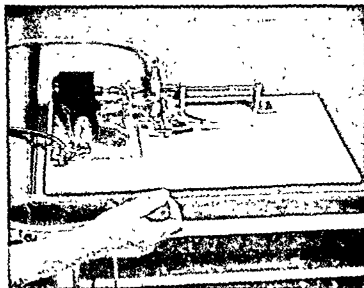


Fig 44 Ergograph

The ergograph as described above may be influenced by the subjective reactions of the patient tested An electronic ergogram may be used to record the motion of the limb muscle when the proper nerve is stimulated. This is a more involved procedure but is very helpful in reducing the subjective response of the patient.

Red Glass Test

The red glass test can be used to measure diplopia. A prism measuring apparatus may be used to determine the degree of prism required to reduce the diplopia to zero.

Barium Swallow

In cases of dysphagia, the weakness of the pyriform muscles of the pharynx can be studied by fluoroscopic observation of a barium swallow[13] Ideally, the barium swallow is performed 12 hours after the last dose of anticholinesterase medication, but this time may need shortening because of the clinical response of the individual patient. Edwards and Murra recommend examination in the erect position and use of a thin bari mixture If the results of the swallow are inconclusive, they repeat t examination with the patient in the prone position and use a thick bariu paste The muscles involved in dysphagia are those of the tongue and cricopharyngeus[44] The test is positive for myasthenia when the followin appear. hesitation in starting deglutition, slow, labored movements of the tongue, breaking up of the bolus and piecemeal swallowing, with pooling in the valleculae and pyriform recesses and tendency to nasal reflux. These findings disappear on a repeat test after administration of anticholinesterase medication, thereby verifying the diagnosis. When x-rays are to be taken, Prostigmin 1 mg intramuscular is preferred. When fluoroscopy only is performed, Tensilon, 2 mg intravenously, is the drug test of choice.

ELECTRICAL TESTS

Changes in electrical responses were noted in patients with myasthenia gravis as early as the mid-nineteenth century Stimulating an individual muscle with faradic current is known as the *Jolly* test. A normal mus will remain contracted for a minimum period of five minutes, whereas myasthenic muscle will become exhausted in less than five minutes (usu ally in one or two)

Electromyography

Electrodiagnosis consists of two procedures electromyography, in which the electric activity produced by muscle is studied, and electric stimulation, in which the response of nerve and muscle to electric stimuli is observed[20] These procedures, alone or in combination, are used in the diagnosis of myasthenia gravis[45,46] Their value is in eliminating subjective responses Electromyography does not give a clinical diagnosis, although

there are wave forms which are pathognomonic of specific disease entities. Electromyography aids in diagnosis when the evidence of abnormality of the motor unit which it reveals is or is not compatible with the clinical diagnosis under consideration The electromyographic results must be integrated with the results of other tests, the clinical examination, and the history in arriving at a diagnosis [20]

In testing for the presence of myasthenia, the usual technique consists of placing electrodes on the surface or insertion of a coaxial needle elec- [illegible]

of three, five or ten single shocks at rates of three, five, ten or twenty-five per second or repetitive stimulation (tetany) of the peripheral nerve are then given. The greater and the more frequent the number of shocks, the more likely it is that the myasthenic phenomenon will be elicited. Because of the discomfort attendant upon frequent and numerous shocks, it is best to start with groups of three and increase as necessary It is always important to test muscles that are affected by myasthenia. Occasionally, the characteristic response of the disorder may be elicited in muscles that are not clinically weak As has been pointed out by many authors, the onset of myasthenia gravis may not involve the muscles of the extremities but may be confined to those innervated by the cranial nerves, especially the extraocular and periorbital muscles In this instance, the Jolly test or the routine electromyogram from an extremity may give no clue in the early diagnosis of this condition Thus, electromyography has been described for other skeletal muscles, for example, the orbicularis oculi.[47] As with other tests, the patient must be examined in a basal state

Criteria for a Positive Electromyography Test

1. Variability in the size of single motor unit action potential on voluntary contraction

2 On repetitive stimulation in the normal patient, the amplitude of the resultant action potential does not decrease In the myasthenic, there is a gradual reduction in amplitude, and toward the end of stimulation, at times, there is skipping of some action potentials.

3 Repair of the defect described above follows maximal isometric exercise, with return to the pre-exercise state in 45 to 60 seconds.

4 Repair of the defect by the administration of anticholinesterase drugs

5 Elicitation of criteria 1 and 2 by the administration of d tubocurarine in proper dosage

6 Post tetanic facilitation, in which there is an increase in muscle action potential response to a single nerve stimulus given after a series of tetanic stimulation, may be another diagnostic criteria.

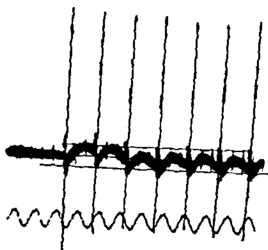


Fig 45. Electromyography Single shocks Normal

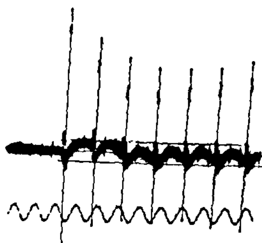


Fig 46 Electromyography. Single shocks Myasthenia gravis.

Electromyography is not required as a routine diagnostic procedure. The pharmacologic tests described above are usually reliable and relatively simple to perform in the clinic or office Electromyography may be of value when the results of other tests are equivocal or when objective tests are needed because of difficulty in interpreting clinical data even though compared with a placebo test.

Breinin [49,51] has developed a technique combining electromyography without stimulation and the Tensilon test This technique requires the

subconjunctival insertion of fine gauge, concentric electrodes directly into the extraocular muscles, using only topical anesthesia This is a simple, practical procedure, devoid of harmful effects, the only complication is the occasional occurrence of a subconjunctival ecchymosis, which is a cosmetic blemish of brief duration The muscle action potentials are suitably amplified, displayed on dual beam oscilloscopes and recorded with moving film photography. The utilization of electromyography to evaluate drug action has revealed a striking and characteristic muscle response even though gross improvement in motility may not be evident.



Fig 47. Electromyogram of extraocular muscle in a nonmyasthenic Line B shows lack of response to Tensilon. (Courtesy of Dr G Breinen)

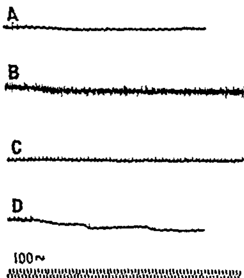


Fig 48 Electromyogram of extraocular muscle in a myasthenic Line B shows positive response to Tensilon. (Courtesy of Dr G Breinen.)

He found no typical myasthenic response to Tensilon in cases of progressive nuclear ophthalmoplegia or in the normal subject.

Breinin used his technique on two cases which presented problems in diagnosis. The first was a 57 year old, white female who presented left ptosis and was said to have had a positive Tensilon test. At examination, no evidence of improvement after Tensilon could be found. The patient gave a history of having had diabetes of many years duration Her blood sugar was 254 mg. per cent. The diagnosis of diabetic neuropathy was made and confirmed by Breinin's technique

Case 6, a patient described in the Chapter on Clinical Aspects who showed resistance to correction of diplopia with anticholinesterase medication, was examined by this technique, and the qualitative myasthenic response confirmed the diagnosis of myasthenia gravis.

Although the technique is simple, it requires a well-equipped endowed laboratory. The test is unquestionably valuable in patients in whom a definitive diagnosis cannot be made.

Viets and Schwab,[52] reporting on a twenty-year experience with the Prostigmin test, state they used the test in 1,500 cases and diagnosed 500 cases of myasthenia gravis They used the intramuscular test routinely, but have also used the intravenous Prostigmin and Tensilon tests They did not find that the intravenous Prostigmin test was of any greater value than the intramuscular test.

In their opinion, any anticholinesterase drug test will be clearly positive in 85 per cent of patients with myasthenia gravis. When the results of the first test are not conclusive, repetition of the test and the use of mechanical means for objective measurements will establish the diagnosis in an additional ten per cent. In the remaining five per cent, placebo tests and objective tests are necessary to establish the diagnosis At times, in this last group, they resorted to the curare test, electronic ergography or electromyography with stimulation The 1,000 patients with a negative response had all been referred with a possible diagnosis of myasthenia gravis. Hoefer,[52] in discussing this paper, stated that in his experience he had had no difficulty in making a diagnosis in 95 per cent of the cases he had tested.

No therapeutic test is absolutely pathognomonic. Hysteria can simulate almost any symptomatology known. In myasthenia gravis, to rule out false-positive responses, placebo testing can be done To rule out false-negative responses, any syndrome of muscle weakness not accompanied by alteration of tendon reflexes in which there is some improvement of strength after administration of correct amounts of Prostigmin or Tensilon should be considered to be myasthenia gravis A history of remissions in the past or evidence of thymic abnormality tends to confirm the diag-

nosis.[53] A positive Tensilon or Prostigmin test serves to confirm the clinical impression derived from the history and physical examination When the technique described above with placebo tests, mechanical and electrical measurements is used, the diagnosis rarely remains in doubt.

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CHAPTER VI

Differential Diagnosis

This section is concerned with both the specific and general differentiation of myasthenia from medical and neurologic disorders in cases in which the clinical picture is not classic in its development. The wide variability in the age of onset of myasthenia, the presence of periods of remission, at times the constant localization of symptoms to certain areas, the production of symptoms resulting from muscle weakness without recognition of such underlying weakness, and the atypical response to medication, all of these factors may serve to confuse the examiner. For example, the periods of remission in myasthenia may simulate multiple sclerosis. Isolated bulbar symptoms in the course of myasthenia may resemble bulbar poliomyelitis, amyotrophic lateral sclerosis, pseudobulbar palsy, and encephalitis, as well as multiple sclerosis. Isolated ocular symptoms may also be found in infectious cranial neuropathies, as seen in diabetes, diphtheria, lues, in certain intracranial neoplasms, and in the so-called Guillain-Barré syndrome. Weakness limited to the limbs and trunk may simulate muscular dystrophy, motor neuropathies, or amyotonia congenita. Almost any myasthenic symptoms, although unaccompanied by demonstrable muscular weakness, may be seen in the picture of psychoneurosis where conversion somatic phenomena, especially neurasthenia, may be the main feature.

Although the dynamic biochemical and neurophysiologic basis of myasthenia is becoming clear, the primary origin of this disorder is still unknown. Diagnosis depends upon the clinical syndrome and special tests with anticholinesterase drugs which are primarily clinical rather than laboratory in their significance. So-called myasthenia-like syndromes with other illnesses have been reported in the literature.[1]

Patients with chronic fatigue may simulate true myasthenia, but they do not have the same responses to testing. There are patients with endocrinopathies or, as recently reported by Eaton,[1,1a] with a myasthenia gravis-like syndrome related to a small cell malignancy of the lung. There are also patients with atrophied or dystrophic muscles who appear myasthenic and the question of whether there is a dystrophic form of myasthenia gravis or whether there is a myasthenic syndrome associated with muscular dystrophy must be resolved

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defect in transmission across the neuromuscular junction. Fatigue is characterized by a progressive reduction in the number of motor-unit action potentials without any appreciable change in the size of potentials, whereas the unusual fatigue of myasthenia gravis has both a progressive decline and a variation in the amplitude of successive potentials. They further state that this latter, unusual type of fatigue as seen electromyographically is not pathognomonic of myasthenia gravis, but can be observed at times in amyotrophic lateral sclerosis, poliomyelitis, progressive muscular atrophy and syringomyelia. In such non-myasthenia gravis cases, electromyographic evidence has been obtained to indicate that the transmission defect may be increased by small doses of curare and improved to some extent by therapeutic doses of anticholinesterase drugs such as Tensilon and Prostigmin. The effects of these two groups of drugs have produced changes in strength detectable by clinical tests even though these conditions could not be classified as myasthenia gravis. Eaton and Lambert state that despite their previous publication[2] to the contrary, they no longer hold the view that positive results to tests for myasthenia gravis with Prostigmin, Tensilon and curare are themselves pathognomonic of myasthenia. They also state that electromyography is often superior to clinical observation in the detection or exclusion of disease of the neuromuscular junction.

In a publication from the Mayo Clinic, the same authors[3] point out that electromyography aids in diagnosis when the revealed defect is compatible with the clinical diagnosis. The pharmacologic tests show only partial repair electromyographically and seldom cause significant clinical improvement in conditions other than true myasthenia gravis. Briefly stated, there is qualitative similarity but distinctly different quantitative effect. Total evaluation, as outlined in Chapter V, is essential to the diagnosis of myasthenia gravis.

Slossberg[4] performed quantitative Tensilon tests using the ergogram and placebo tests on five known amyotrophic lateral sclerosis patients, injecting up to 20 mg. of Tensilon chloride, but no improvement in the ergogram was seen. In fact, the hand grip strength decreased somewhat with the larger doses of Tensilon, even though the patient subjectively felt better. Fasciculations which were spontaneously present became much more exaggerated with Tensilon.

The myasthenic aspect of some of these illnesses cannot be denied and they are possibly related etiologically or pathophysiologically to myasthenia. It is preferable to apply the term myasthenia gravis only when the characteristic syndrome is demonstrated. As has been shown in previous chapters, this does not mean that each patient must have all the classical symptoms or be gravely ill.

As discussed in the Chapter on Diagnosis, about one-third of patients referred with symptoms suggestive of myasthenia gravis will be diagnosed finally as having this illness[5,6] Errors in diagnosis may be due to false-positive or false-negative test results. The greatest errors are in the former group and are due to inexperience with this problem, the diagnostician depending too much on the subjective reactions of the patient. Objective tests such as the ergogram are the best means of avoiding false-positive reactions, but even these tests may be modified by suggestible patients. Placebo testing is important in evaluating diagnostic tests. False negatives are rare, but do occur when either insufficient objective response is noted or overdosage with the testing drug causes a cholinergic reaction. This results in weakness so that the examiner fails to appreciate the improvement that can be obtained with proper dosage

In general terms, myasthenia is an illness of muscular weakness which must be differentiated from weakness caused by interruption of function along any portion of the motor pathway from motor cell in the brain to the effector organ itself, the muscle. We must differentiate myasthenic weakness from the weakness of pyramidal tract disease, anterior horn cell disease, motor peripheral nerve pathology and involvement of the muscle itself.[5-13]

Limb Weakness

Weakness in pyramidal tract disease is accompanied by spasticity of muscle, over-active deep tendon reflexes, absence of superficial reflexes, and the presence of such pathologic reflexes as the Babinski sign Weakness resulting from anterior horn cell disease is accompanied by atrophy of muscle, the presence of discernible fasciculations and the absence of deep reflexes. The weakness secondary to involvement of the motor peripheral nerve does not vary with rest and effort, is not accompanied by fasciculations, may result in ultimate atrophy and is accompanied by diminished to absent deep tendon reflexes

Primary muscular weakness as seen in muscular dystrophy and dermatomyositis is characterized by unremitting weakness, absence of fasciculations, normal to depressed reflexes based upon the severity of the weakness and ultimate atrophy in long-term cases.

In the myasthenic, weakness fluctuates in severity dependent upon the rest-effort state. There is usually no accompanying atrophy, fasciculations are not found and the deep tendon reflexes are generally within normal limits unless the muscular weakness is so severe that the effector organ cannot respond With these clinical characteristics in mind, there should be no great difficulty involved in differentiating myasthenic weakness from the other causes of weakness if the limbs are affected.

Bulbar Weakness

Many myasthenic patients at one time or another during the course of their illness exhibit symptoms of bulbar muscle involvement This may consist of dysarthria, dysphagia, dysphonia, or respiratory difficulties This bulbar syndrome, for purposes of clarity, is confined to the muscles innervated by the medulla oblongata A number of conditions may present bulbar symptoms identical to the symptoms of bulbar myasthenia and will require differentiation

When a patient is seen for the first time with bulbar symptoms, the physician should distinguish between bulbar poliomyelitis, the bulbar palsy seen with amyotrophic lateral sclerosis, progressive bulbar palsy, pseudobulbar palsy and the bulbar syndromes seen in encephalitis and multiple sclerosis Muscular dystrophy does not produce bulbar involvement except in extremely rare instances

Acute anterior poliomyelitis with bulbar involvement can be confused with an acute bulbar form of myasthenia gravis with respiratory involvement because of the similarity of presenting symptoms Acute poliomyelitis is accompanied by fever, severe headache, nuchal rigidity, and usually rather symmetric involvement of other muscles as well The spinal fluid in acute bulbar poliomyelitis is generally abnormal, showing at least the presence of a small number of white cells In myasthenia the spinal fluid is within normal limits The potential confusion between acute bulbar polio and acute bulbar myasthenia was epitomized a few years ago by a Buffalo physician [14] who wrote that he administered a Tensilon test to a patient considered to have acute bulbar polio and found marked improvement. The patient was subsequently treated with anticholinesterase medication and symptoms were relieved The confusion in this particular instance was the result of the existence of a polio epidemic in the area and the fact that the myasthenic patient had a febrile reaction and respiratory weakness. It therefore becomes rather important during epidemics of poliomyelitis to be aware of the fact that atypical problems may conceivably be myasthenic in origin A Tensilon test or additional diagnostic procedures may clearly demonstrate the differential diagnosis

The bulbar symptoms caused by involvement of the motor cells of the medulla, as seen in progressive bulbar palsy or amyotrophic lateral sclerosis, is easily differentiated from the pseudobulbar palsy seen in diffuse hypertensive-arteriosclerotic disease of the brain, especially that with involvement of the internal capsules bilaterally Both of these conditions, in turn, though presenting similar symptoms, are easily differentiated on clinical grounds from the picture of bulbar myasthenia When amyotrophic lateral sclerosis or progressive bulbar palsy involves the

motor cells of the medulla, the symptoms of bulbar involvement are accompanied by atrophy of the tongue, fibrillations of the tongue, absence of the jaw jerk, and absence of the palatal reflex. In pseudobulbar palsy, although the presenting symptoms may be identical to those of bulbar palsy, the tongue is not atrophied, there are no involuntary movements of the tongue, and the jaw jerk and palatal reflexes are hyperactive Bulbar palsy with amyotrophic lateral sclerosis is ordinarily accompanied by other evidences of bilateral involvement of both anterior horn cells and pyramidal tracts, as will be noted later. Pseudobulbar palsy is generally accompanied by diffuse evidence of brain disease, including extensive pyramidal tract involvement of the limbs. In multiple sclerosis and acute encephalitis the involvement of the brain stem and the medulla chiefly concerns the corticobulbar tracts, so that the clinical picture is essentially that of pseudobulbar palsy as described above. In bulbar myasthenia there is the characteristic phenomenon of the disorder: improvement of symptoms with rest and anticholinesterase medication and increasing weakness with effort.

Isolated Ocular Symptoms

Isolated ocular symptoms, either ptosis or diplopia, are found in many neurologic disorders Characteristic of the strabismus seen as a congenital or heredodegenerative process is the static nonprogressive nature of the ocular sign from birth on But even this need not be an absolute differentiation A patient has been seen who had a congenital strabismus of the external type, superimposed upon which myasthenia developed, increasing only the degree of external rotation of the left eyeball and demonstrable only by the response of the eyeball to anticholinesterase medication Congenital ptosis of the lids is perhaps most often confused with myasthenia gravis, but this too is a disturbance exhibited at birth and nonprogressive in nature In these cases the familial history, static nature of the ptosis, history of its presence since birth, as well as the negative responses to anticholinesterase medication serve to differentiate the condition from myasthenia

Involvement of the oculomotor, trochlear, or abducens nerves by any number of processes, including infections, trauma and neoplasm, produce characteristic ocular palsies which do not have the fluctuating characteristics of myasthenia The myasthenic involvement of external ocular muscles may very closely simulate any of the ocular palsies. It has been said that when myasthenia discretely involves one eye in a manner which produces what appears to be a typical third nerve palsy, the differential point of significance is the absence of involvement of the pupil Since peripheral involvement of the oculomotor nerve is almost invariably ac-

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companied by an internal ophthalmoplegia as well as an external ophthalmoplegia, this is used as a distinguishing characteristic There have been reports in the literature of isolated cases of myasthenia involving the ciliary muscle In such rare instances the ultimate differentiation may depend upon the response to medication

When diplopia and/or ptosis are accompanied by localized headache over the involved eye or by pain in the eye, one must think seriously of an intracranial aneurysm If there is diminished corneal sensation in the involved eye, this diagnosis becomes a probability and myasthenia is excluded In the cranial neuropathies associated with diabetes, lues, diphtheria and the Guillian-Barré syndrome, the total clinical picture is essential for the differentiation of these conditions from myasthenia If myasthenia is still suspect, the response of symptoms to medication again becomes the diagnostic factor. In multiple sclerosis, ocular symptoms are most often accompanied by nystagmus, and true nystagmus is rarely seen in myasthenia The nystagmus of multiple sclerosis origin results most often from involvement of the median longitudinal bundle, with resultant horizontal and vertical nystagmus, diagnostic of involvement of the brain stem

Unilateral ptosis as an isolated sign or symptom may be congenital or due to involvement of the ocular sympathetic nerves or the oculomotor nerve, or it may be myasthenic in origin Congenital ptosis as previously described exists from birth and does not vary Involvement of the ocular sympathetic nerves produces a Horner's syndrome in which case the ptosis is accompanied by ipsilateral miosis, enophthalmos and diminished sweating over the same side of the head and face Ptosis produced by third nerve palsies as previously noted, is accompanied by dilatation of the pupil as well as specific ocular palsies related to involvement of the third nerve In these cases the eye is commonly deviated externally because of the unopposed pull of the external rectus muscle The diagnosis of myasthenia is confirmed by the response of ptosis to medication.

The differential diagnosis of myasthenia includes the consideration of a number of medical and neurologic disorders To complete this discussion, a brief description of the clinical picture of some of these disorders may help to clarify the differential diagnosis

Differentiation from Other Diseases

Progressive Ophthalmoplegia

Progressive ophthalmoplegia is characterized by a progressive paralysis of the extraocular muscles of the eye without evidence of disease else-

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Unilateral ptosis as an isolated sign or symptom may be congenital or due to involvement of the ocular sympathetic nerves or the oculomotor nerve, or it may be myasthenic in origin Congenital ptosis as previously described exists from birth and does not vary Involvement of the ocular sympathetic nerves produces a Horner's syndrome, in which case the ptosis is accompanied by ipsilateral miosis, enophthalmos and diminished sweating over the same side of the head and face Ptosis produced by third nerve palsies, as previously noted, is accompanied by dilatation of the pupil as well as specific ocular palsies related to involvement of the third nerve In these cases the eye is commonly deviated externally because of the unopposed pull of the external rectus muscle The diagnosis of myasthenia is confirmed by the response of ptosis to medication

The differential diagnosis of myasthenia includes the consideration of a number of medical and neurologic disorders To complete this discussion, a brief description of the clinical picture of some of these disorders may help to clarify the differential diagnosis

Differentiation from Other Diseases

Progressive Ophthalmoplegia

Progressive ophthalmoplegia is characterized by a progressive paralysis of the extraocular muscles of the eye without evidence of disease else-

motor cells of the medulla, the symptoms of bulbar involvement are accompanied by atrophy of the tongue, fibrillations of the tongue, absence of the jaw jerk, and absence of the palatal reflex In pseudobulbar palsy, although the presenting symptoms may be identical to those of bulbar palsy, the tongue is not atrophied, there are no involuntary movements of the tongue, and the jaw jerk and palatal reflexes are hyperactive Bulbar palsy with amyotrophic lateral sclerosis is ordinarily accompanied by other evidences of bilateral involvement of both anterior horn cells and pyramidal tracts, as will be noted later Pseudobulbar palsy is generally accompanied by diffuse evidence of brain disease, including extensive pyramidal tract involvement of the limbs. In multiple sclerosis and acute encephalitis the involvement of the brain stem and the medulla chiefly concerns the corticobulbar tracts, so that the clinical picture is essentially that of pseudobulbar palsy as described above. In bulbar myasthenia there is the characteristic phenomenon of the disorder. improvement of symptoms with rest and anticholinesterase medication and increasing weakness with effort.

Isolated Ocular Symptoms

Isolated ocular symptoms, either ptosis or diplopia, are found in many neurologic disorders Characteristic of the strabismus seen as a congenital or heredodegenerative process is the static nonprogressive nature of the ocular sign from birth on But even this need not be an absolute differentiation A patient has been seen who had a congenital strabismus of the external type, superimposed upon which myasthenia developed, increasing only the degree of external rotation of the left eyeball and demonstrable only by the response of the eyeball to anticholinesterase medication Congenital ptosis of the lids is perhaps most often confused with myasthenia gravis, but this too is a disturbance exhibited at birth and nonprogressive in nature In these cases the familial history, static nature of the ptosis, history of its presence since birth, as well as the negative responses to anticholinesterase medication serve to differentiate the condition from myasthenia

Involvement of the oculomotor, trochlear, or abducens nerves by any number of processes, including infections, trauma and neoplasm, produce characteristic ocular palsies which do not have the fluctuating characteristics of myasthenia The myasthenic involvement of external ocular muscles may very closely simulate any of the ocular palsies. It has been said that when myasthenia discretely involves one eye in a manner which produces what appears to be a typical third nerve palsy, the differential point of significance is the absence of involvement of the pupil. Since peripheral involvement of the oculomotor nerve is almost invariably ac-

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may be inherited in different ways As yet, we do not know the nature of the hereditary fault, whether it lies in the structure of the muscles per se or in a disorder of metabolism or in endocrine control or other factors Trauma and infection have been followed by the development of dystrophy, but it is most probable that they are only precipitating factors in an individual constitutionally predisposed to dystrophy.

Associated endocrine disturbances occur. These may be hypo- or hyperfunction of one gland, but more frequently there is partial pleurae glandular dysfunction. It has been known for many years that there is a defect in the creatine metabolism of dystrophic patients It is possible that this disturbance in creatine metabolism is merely an expression of muscular wasting Milhorat and co-workers[19] found that in muscular dystrophy creatine tolerance is impaired After an oral dose of 1 to 3 grams of creatine, it can be recovered in the urine A normal person would store this oral dose of creatine in the muscles without excreting any in the urine Shank, Gilder and Hoagland[20] reported only slightly impaired creatine tolerance in their pediatric patients Some investigators feel that creatinuria is to dystrophy what glycosuria is to diabetes[21] Experience has demonstrated, however, that it is much less specific

Recent evidence suggests a disturbance in the enzyme systems concerned with muscle metabolism, one of the tocopherols perhaps playing an important role

Pathology Early pathology is the swelling of some muscle fibers and increase in sarcolemma nuclei The striation becomes less marked After early changes, a number of very small muscle fibers are found which may be due to splitting of the hypertrophied fibers Muscle fibers undergo degeneration and conversion into fibrous tissue The connective tissue septa between the fibers are increased and there is marked interfibrous deposition of fat, which is the basis for the increased bulk of the pseudohypertrophied muscle Infiltration with round cells and even multinucleated cells is sometimes present

Chemical analyses of dystrophic muscles have been reviewed by Nevin[22] A decrease of creatine, acid soluble phosphorus, phosphocreatine and adenosine triphosphate has been reported, indicating the loss of definite muscle compounds without relationship to the disease The breakdown and resynthesis of phosphate compounds has been reported to occur as readily as in normal muscle

Symptomatology Symptoms of dystrophy are essentially those due to muscular weakness In the majority of cases, girdled musculature is more severely affected than that of the distal parts of the extremity Weakness of the pelvic girdle muscles gives rise to the characteristic waddling gait The patient is clumsy in walking and has difficulty in climbing up and

where in the nervous system The onset is usually in early childhood, but may occur in the twenties or thirties. Progressive ophthalmoplegia has a *high familial incidence. The onset is usually a slight* ptosis of the lids which progresses slowly over a number of years to complete ophthalmoplegia Occasionally, the onset is only in one eye, with a delay of several years before it becomes bilateral The pathology and etiology of this condition are not clearly understood. There have been few pathologic examinations performed

Recently, investigators [15-17] have been in favor of considering this condition as part of the clinical syndrome of progressive muscular dystrophy The course of the disease is progressive, with an occasional spontaneous arrest The duration of life is not affected

The differential diagnosis of myasthenia may at times seem difficult, particularly in the juvenile form which exhibits complete ophthalmoplegia and has a fairly high familial incidence. Usually, in the juvenile form of myasthenia other muscle groups are involved which respond to the specific cholinesterase inhibitors In early cases there are distinct differences in response of the extraocular muscles to electromyography. When the myasthenia has existed for a long period of time and is associated with some atrophy of the muscle, the electromyographic differentiation is quantitative rather than qualitative The differentiation is determined by the electromyographic response to anticholinesterase drugs.

Muscular Dystrophy

Muscle atrophy can occur as a result of malnutrition, immobilization of a limb by cast, infections of the joint, trauma, inflammatory diseases of the muscles, diseases of the peripheral nerve or spinal cord, or various metabolic disorders such as hyperthyroidism This type of atrophy is almost always secondary in nature and has an obvious, adequate explanation of its origin.

Progressive muscular dystrophy [18] has been used as a term to describe a group of disorders with characteristic pathologic changes in the involved muscles without demonstrable lesions in the nervous system *Muscular dystrophies are a group of disorders* in which the essential feature is a progressive degeneration of certain groups of muscles The [illegible] types of [illegible]

that each group represents a distinct disorder.

Etiology A congenital and, in many cases, hereditary abnormality is the primary cause of the dystrophy The mode of inheritance of the disorder is not completely understood, but it appears that different forms

2 The *mild restricted* is a slowly progressive, proximal myopathy involving primarily the musculature of the shoulders and often the face, with long remissions and often complete arrest, and weak familial incidence Onset can be as early as two years of age and as late as sixty, but commonly occurs in the twenties It affects sexes equally The best-known form is the facioscapulohumeral dystrophy.

3 *Progressive dystrophic ophthalmoplegia* is a very slowly progressive myopathy involving primarily, and usually limited to, the levators of the eyelids and the external ocular muscles, resulting in ptosis and ophthalmoplegia, with familial incidence in half the cases

4 *Dystrophic myotonia* is a steadily progressive, familial, distal myopathy with associated weakness of the muscles of the face and levators of the eyelids and a tendency to myotonic persistence of contraction in the affected parts, with testicular atrophy, other disorders of endocrine glands, and frequent cataract

Differential Diagnosis There is very little likelihood of confusing muscular dystrophy and myasthenia gravis except in the case of progressive dystrophic ophthalmoplegia in which ptosis and ophthalmoplegia and the masklike face give a first impression of possible myasthenia gravis This may also occur to some extent in the mild restricted and dystrophic myotonia forms When atrophy occurs in Group V myasthenia gravis, this tends to confuse the diagnosis

The differential diagnosis between muscular dystrophy and myasthenia gravis can be made on the basis of the following findings

1 There is much greater tendency to muscle atrophy in dystrophy than in myasthenia

[illegible]

culature, with a typical involvement of the muscles of the eyes, chewing and swallowing, which is rarely present in dystrophy[23]

5 Reaction to faradic current in myasthenia is either normal or a typical Jolly reaction

[illegible]

in the extraocular muscles

[illegible]

lon test Only the myasthenic patient shows improvement upon testing, the dystrophic patient never does

down stairs Weakness of the shoulder girdle makes it difficult to raise the arms over the head or lift heavy objects. Pain is rarely present and there are no sensory symptoms

Physical Examination When the facial muscles are affected the expression is sardonic. The eyes are imperfectly closed in sleeping, and facial movements are absent Laughing, crying or whistling is difficult. Involvement of ocular, masticator, palatal and pharyngeal muscles is relatively rare

In the majority of cases, dystrophy is limited to the muscles of th- trunk and extremities Pseudohypertrophy may be present in all th muscles of an extremity or may be entirely absent More often, atrophy and pseudohypertrophy occur in different muscle groups. The gastrocnemius, deltoid and triceps are most frequently affected by pseudohypertrophy.

There may be an advanced degree of lumbar lordosis Movement of arms may show winging of the scapula. When attempting to lift a c by placing the hands in the axilla, the child may slip through the ha because of weakness of the shoulder girdle muscles. When the pati rises from the supine to the erect position, he does so in a typical manne first turning onto the abdomen and then raising the trunk to the crawling position He then places the feet firmly on the floor with the aid of his arms and gradually elevates the upper part of the body "by climbing his own trunk with his arms" When the disease is more advanced, the patient is able to rise from the floor only by pulling himself up with his hands with the aid of some fixed object

On palpation, hypertrophied muscles feel firm and rubbery. Atrophic muscles are often difficult to feel because of the overlying fat Involvement of musculature is usually symmetric The degree of weakness of the two sides usually varies, but involvement limited to one side does not occur Abnormal movements are not present and fibrillary twitching of muscles occurs only in rare cases.

Sensory examination is normal There are no sphincter disturbances Deep reflexes may be lost early in the course of the disease or they may persist in the atrophied muscle Knee jerks usually disappear before an jerks Cutaneous reflexes are intact and the Babinski toe sign is abse. Response of muscles to faradic or galvanic current is quantitatively r duced and is lost when muscles are completely atrophied.

Types There are four forms of muscular dystrophy.[13]

1 *Severe generalized familial* is most common It is a rapid, progressive type of myopathy beginning usually in early childhood, with strong familial tendency, and occurring predominantly in males, with or without pseudohypertrophy.

2 The *mild restricted* is a slowly progressive, proximal myopathy involving primarily the musculature of the shoulders and often the face, with long remissions and often complete arrest, and weak familial incidence Onset can be as early as two years of age and as late as sixty, but commonly occurs in the twenties It affects sexes equally The best-known form is the facioscapulohumeral dystrophy

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1. There is much greater tendency to muscle atrophy in dystrophy than in myasthenia

2 Pseudohypertrophy of the muscle occurs only in dystrophy

3 The dystrophic patient tends to lose the deep reflexes. Deep reflexes are [illegible]

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5 Reaction to faradic current in myasthenia is either normal or a typical Jolly reaction

[illegible]

in the extraocular muscles

[illegible]

lon test Only the myasthenic patient shows improvement upon testing, the dystrophic patient never does

Myotonia Congenita

Myotonia congenita is a rare disease characterized by myotonic reaction, i.e., a tonic cramp during "willed" muscular movement. It is always hereditary. There are no dystrophic features. The sexes are equally affected. There is more or less pronounced muscular hypertrophy and all skeletal muscles are affected, as distinct from dystrophic myotonia. The picture of myotonia as elicited not only by the history of difficulty in relaxation of contracted muscles but also by simple mechanical stimulation of the tongue, adductor muscle of the thumb, or extensor mass of the forearm, is almost diametrically opposed to that of myasthenia. As a matter of fact, the muscle response in these illnesses to anticholinesterase drugs or quinine is precisely opposite, i.e., anticholinesterase drugs produce improvement in myasthenia and exacerbation in myotonia, whereas quinine produces exacerbation in myasthenia and some improvement in myotonia.

Poliomyelitis

Acute poliomyelitis is ordinarily a syndrome never confused with myasthenia except when myasthenia is initiated by bulbar symptoms. The similarities and distinction between bulbar myasthenia and bulbar poliomyelitis have been discussed previously.

Multiple Sclerosis

Multiple sclerosis is a chronic neurologic disease characterized pathologically by the presence of numerous areas of demyelinization in the central nervous system and clinically by a variety of neurologic symptoms and signs which have a tendency toward spontaneous remission and exacerbation. It is fairly common, having been reported as occurring in two to ten per cent of patients with organic nerve disease.[8] The mean age of onset is 28 years, the earliest being about 4 years and the latest at 65. There have been various reports on sex differences, some reporting its presence to be more common in females while others have found it predominant in males. MacKay[27] found no evidence for a difference between the sexes in incidence.

Etiology. The cause of multiple sclerosis is not known. The disease has been stated to be due to infection, toxins, trauma, metabolic fault and allergy. The lesion has been produced experimentally by many of the above-mentioned excitants. The possibility of an inherited predisposition has been studied and an incidence of 6.5 per cent family history has been reported.[28] Precipitating factors have been described, usually infections such as influenza, specific fevers, pregnancy, surgical operation, dental

extraction, carbon monoxide poisoning or electric shock.[29] McAlpine and Compston[29] obtained a history of trauma in 14.4 per cent, whereas in controls the figure was 5.2 per cent. They also found some evidence of a relationship between the site of the trauma and the site of the first symptom.

From the various investigations, it would seem that disseminated sclerosis may be essentially a type of reaction to a number of etiologic facts. Sclerosis is but the end-stage of inflammation and lacks the property of etiologic inference. Dublin[8] states that the term disseminated sclerosis doubtless will be replaced in the future by the term disseminated encephalomyelitis of various causes when the etiologic factors are discovered.

Pathology. The gross neuropathologic picture varies with the stage of the disease. In the advanced stage, generalized cerebral atrophy is apparent but is not equal to that seen in paresis or senility. This atrophy results largely from shrinkage of the white matter. Distributed widely throughout brain and spinal cord, as well as cranial and spinal nerve roots, are foci of tissue alteration. The optic nerves, chiasm and tracts are often involved. Throughout the lesions the white matter is preponderantly affected, but there is spread to gray matter without respect to anatomic boundary, zone of blood supply or functional division, the common denominator being that both the gray and white matter contain myelinated fibers. The acute plaques are edematous and bluish red from congestion and anoxia. Hemorrhages are infrequent. Lesions of a few weeks' duration are characteristically yellow due to the liberation of fat and tend to be soft as a result of necrosis. The mature sclerotic plaque is gray, translucent and firm. All stages of the inflammatory process may be seen in a single plaque.

Microscopically, the early lesion shows congestion, especially of the venules, with perivascular edema. A few venous thrombi have occasionally been found at an early stage. There is little or no endothelial swelling or obliterative hyperplasia. The next stage is tissue destruction in which myelin suffers. Axis cylinders are little damaged and cellular response is mild in the early case. In the more severe case the myelin sheath fragments into discrete globules with the liberation of fat. Lymphocytes are present in moderate numbers and, in severe forms, even polymorphonuclear cells may appear. In the more severe cases the damaged axis cylinders are swollen, tortuous and fibrillated and may even disintegrate completely. As the inflammation subsides, astrocytes proliferate about the foci of degeneration, depositing glial fibrils along the course of the damaged nerve fibers and producing an isomorphic form of gliosis. The cerebrospinal fluid is normal in one-half the cases. In the acute case there tends to be a mild lymphocytosis of 6 to 40 cells, al-

though counts as high as 300 have been reported. The protein is slightly to moderately increased in the range of 47 to 75 mg. per 100 ml. A first-zone gold reduction is present in 25 per cent and a mid-zone in 22 per cent, but the Wasserman reaction is negative. Electrophoresis may show an increased peak in the globulins, particularly of the gamma type.

Signs and Symptoms The signs and symptoms of multiple sclerosis are so diverse that they include almost all possible changes which may occur from damage to the central nervous system. Chief characteristics of the disease are the multiplicity of symptoms and the tendency to vary in severity with the passage of time. There may be complete remission of the initial episode, but after subsequent attacks, remissions are usually incomplete.

The symptoms in the early stages may be those of a single focal lesion, but with the passage of time and the occurrence of new lesions, disability increases The onset of the illness is usually very rapid. In a series of 100 cases, Brain [11] has listed involvement of limbs as occurring in 50, visual symptoms in 29, in which blindness of one eye occurred in 16 and diplopia in 8, sensory symptoms in 11; and 10 had miscellaneous symptoms, including ptosis. Weakness of one of the extremities and disturbances of vision were most common.

Multiple sclerosis patients have been described as showing an intention tremor, scanning speech and amblyopia. The loss of power in the lower limbs is first manifested as fatigue and a feeling of heaviness, later as spastic paraplegia. At times, sudden weakness of one upper limb occurs, often associated with loss of postural sensibility. Facial weakness occurs occasionally. Muscular wasting is very rare, although it may occur in an "amyotrophic" form which involves mostly the forearms and hands. Incoordination is frequently present, elicited in the form of an intention tremor by the finger-to-nose test In the lower extremities incoordination can be observed in an ataxic gait.

There may be tremor of the head in the later stages. Dysarthria may be due to either spastic weakness or to ataxia of the muscles of articulation Articulation may be slurred in the early stages. Later, it may become explosive and the patient may be almost unintelligible. Brain [23] states that the so-called scanning speech which has been regarded as typical is exceptional. Involvement of other cranial nerves, particularly the second, third, fourth and sixth, is reported to occur frequently. Involvement of the optic nerve may lead to blindness, diminution in visual acuity and various types of visual field defects or scotomata. The optic nerve head, on fundoscopy, may be pale and smaller than normal. Optic atrophy was found in 11 per cent and temporal pallor in 65 per cent; the temporal pallor was bilateral in one-half the cases. Involvement of the third, fourth

and sixth nerves leads to ocular palsies which are due to damage within the nuclei or to nerves in the brain stem These palsies are frequently transient, but may be permanent Diplopia appears in about one-third of the cases An important finding is the presence of nystagmus, which has been reported present in the routine examination of over 70 per cent of patients at any stage[9] Loss of vestibular response to caloric stimulation or rotation is rare The nystagmus is most commonly the horizontal type and is elicited on lateral movement of the eye Vertical nystagmus is present in about one-third of the cases Abnormalities in the size, shape and reactions of the pupils to light and accommodation are uncommon in the early stages of the disease In the later stages any abnormality may be present, including the typical Argyll Roberston pupil

A multiplicity of changes may occur in the sensory system, particularly diminution of vibration and position sense, with a dissociation between the degree of involvement of these two senses Minor changes in the sense of pain, temperature and touch are found in a small percentage of cases The cutaneous sensory changes are often transient, but proprioceptive loss is more apt to persist

The deep tendon reflexes are exaggerated in the majority of cases In over two-thirds of the cases the Babinski sign is present bilaterally, although it may be unilateral Ankle clonus is present in one-half the cases The reflex may be absent in the upper or lower extremity in five to ten per cent In the so-called tabetic form, the signs of posterior column involvement predominate, but the planter response may be extensor in type An important and useful sign is the abdominal skin reflexes, which are diminished to absent in 80 per cent, whereas the cremasteric reflexes are usually intact

The autonomic nervous system may be involved, with the onset of a cord bladder in 40 per cent which results in urgency, frequency, difficulty in starting the stream and incontinence. The cord bladder seems to persist The bowel is rarely involved There may be evidence of involvement of the cervical sympathetic nerves, with the presence of a Horner's syndrome

Disturbance in mood in the form of euphoria or depression may occur MacKay[27] has stated that the duration of life in multiple sclerosis is greater than commonly supposed and that the mean duration is twenty years or more

Differential Diagnosis In the early phases of multiple sclerosis and myasthenia gravis there are many common symptoms, including diplopia, generalized weakness, particularly of the extremities, dysarthria and at times facial weakness Both disorders are characterized by spontaneous remission, which can be a point of confusion in differential diagnosis.

Differentiation should be comparatively easy, however, for the following reasons.

In multiple sclerosis the weakness tends to be of a spastic type, whereas in myasthenia it is flaccid The reflexes in myasthenia, both the deep and cutaneous reflexes, are normal, whereas in multiple sclerosis there is usually an exaggeration of the deep reflex and diminished or absent abdominal reflexes. Nystagmus is common in multiple sclerosis but rare in myasthenia gravis The Babinski sign may be present in multiple sclerosis but not in myasthenia. The finger-to-nose test with production of intention tremor, ataxic gait, loss of proprioceptive and vibratory sense are present in multiple sclerosis but not in myasthenia gravis

Dysarthria, though present in both conditions, tends to be different In myasthenia the tone is nasal and volume diminishes on continuous speech. In multiple sclerosis the speech is slurred early and later becomes explosive and almost unintelligible Syllabic or scanning speech may also be present in multiple sclerosis

The cerebrospinal fluid in myasthenia is normal, whereas in multiple sclerosis it may show slight increase in cells, protein, a positive gold curve, and proportional increase in the gamma globulins

In myasthenia gravis there is increase of symptoms with repetitive movements and decrease with rest, which does not occur in multiple sclerosis The myasthenic may have a positive response to the Jolly test, ergograph and electromyograph, but has a normal electroencephalograph. In multiple sclerosis the latter test may be abnormal, but the others may be normal Finally, the myasthenic patient gives a positive response to the Tensilon or Prostigmin test, but the multiple sclerosis patient has a negative response.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis was first described in the mid-1800's by Aran [18] and Duchenne [30] Charcot [31] distinguished two varieties, a progressive muscular atrophy characterized by lower motor neuron lesions and a form associated with symptoms of pyramidal tract involvement. When the medulla alone is involved, the condition may be called progressive bulbar paralysis or palsy. Occasionally, it has been called chronic poliomyelitis because of the involvement of the anterior horn cells of the spinal cord. A rare form involves the ocular motor system and is called progressive ophthalmoplegia

The electric excitability of muscles is decreased and there is hyporeflexia The Werdnig-Hoffman type also occurs in infancy, with weakness of atrophy occurring in the large proximal muscles of the pelvic girdle and extending into the thighs and legs In most cases, however, the symp-

toms of upper and lower motor neuron lesions are mixed and the term amyotrophic lateral sclerosis best describes the condition

Etiology Clinically, there is progressive wasting of the muscles, with evidence of pyramidal tract involvement and the presence of fasciculation of the muscles The etiology is unknown Merritt[9] states that some deficiency in the nutrition of the motor neurons relates to a disturbance in the enzyme system concerned with their metabolism.

Precipitating factors may be trauma, acute infection, nutritional disturbance or exhaustion The incidence is relatively common and there tends to be two males for each female Its onset is in mid-life and heredity seems to play an insignificant part. Currently, the disease is being studied in Guam where there is an unusually high incidence[32]

Pathology Gross examination often is unrevealing There may be grayness of the pyramidal tracts from loss of myelin Microscopically, the pathology is essentially a degeneration of the motor neuron in the spinal cord, brain stem and, to a lesser extent, the cortex, with secondary degeneration of the lateral and ventral tracts of the spinal cord There is usually

motor cranial nerves are atrophic and show loss of myelin and axis cylinders The peripheral nerves show partial degeneration, and the muscle shows varying atrophy of the different fibers, some appearing virtually empty, as sarcolemma sheathes, or as narrow strands Striations are diminished to absent, and atrophic fibers show hydropic vacuolation, with the atrophic muscle tending eventually to be replaced with adipose tissue The most severe damage in the brain stem is found in the nuclei of the eleventh and twelfth nerves and the nucleus ambiguus The cells of the seventh nucleus and the motor fifth and the vestibular nucleus may be affected, but the third, fourth and sixth are usually spared In approximately one-third of the cases the Betz cells in the motor cortex decrease

Signs and Symptoms The clinical picture is dependent on the localization of the pathology, and various syndromes are possible. The disease is usually chronic, but may run a subacute course Onset is frequently insidious The early changes are commonly noted in the hands, which become weak or may develop muscle wasting or fasciculations When the shoulder girdle is involved, there is weakness of the movements of the shoulder When the bulbar motor nuclei are involved, dysarthria and fasciculations of the lips or tongue are the early symptoms It is rare for widespread weakness and wasting to occur without fasciculations When fasciculatons are not spontaneously present, they can be evoked by sharply tapping the muscle

The condition may be symmetric or asymmetric. The tongue and lips are involved early in the bulbar form, but the eye muscles are affected only in the very late stages of the disease, if at all. Protrusion of the tongue is first difficult and later impossible. Speech suffers from paresis of the lips, tongue and palate, resulting first in slurring and finally in unintelligible sounds Phonation suffers late, if at all Swallowing becomes increasingly difficult and foods tend to regurgitate through the nose.

Occasionally, the extensor muscles of the cervical spine are involved early, resulting in the head falling forward Early involvement of the muscles of the lower extremity is rare and may give rise to bilateral foot-drop When symptoms of the upper motor neuron lesion are added to the lower motor neuron lesion, a degree of weakness results which is disproportionate to the amount of wasting, and the deep reflexes become exaggerated in spite of the muscle atrophy. Exaggeration of a normal emotional response in the form of paroxysms of involuntary laughing or crying may occur, chiefly in the pseudobulbar form.

Differential Diagnosis. The appearance of generalized weakness involving the upper extremities, plus dysarthria and dysphagia, as noted before, may cause some confusion with myasthenia gravis. The neurologic picture of increased reflexes, the presence of pyramidal tract signs with muscular wasting and spontaneous fasciculations should clearly differentiate amyotrophic lateral sclerosis from myasthenia gravis The reaction to faradic current is mixed in amyotrophic lateral sclerosis. Since all muscle fibers are not involved, it is not the simple reaction of degeneration When galvanic current is used for stimulation in those cases showing a normal or almost normal faradic response, the phenomenon of polar reversal occurs. Electromyography shows spontaneous fasciculations on mechanical stimulation by the exploring needle [33] Eaton [34] has stated that he has seen patients with amyotrophic lateral sclerosis who improve on Tensilon when fairly large amounts are used. Bender [35] partially confirms this and has had a case in which Mestinon therapy partially improved the patient's ability to stick out the tongue. Quantitative Tensilon tests fail to confirm the value of anticholinesterase drugs in the treatment of amyotrophic lateral sclerosis. In fact, as stated previously, hand grip was diminished when large doses of Tensilon were administered [4]

Periodic Familial Paralysis

Periodic familial paralysis is a rare and peculiar type of intermittent paralysis which begins in childhood and recurs for many years Both

with gradual recovery Bulbar muscles, including those governing respiration, are usually spared The defect is said to be due to a disturbance in potassium metabolism, since low levels are found during an attack Differential diagnosis is made by the familial incidence, history of attacks, lack of bulbar symptoms, or by using the following test to induce an attack breakfast, consisting of 300 grams of carbohydrate is given and 10 units of regular insulin are injected Serial potassium levels will show a fall and a clinical attack may be induced. In two cases of periodic familial paralysis tested with Tensilon, severe cholinergic response was induced, which was reversed with atropine

Hyperthyroid Myopathy

Chronic thyrotoxic myopathy is characterized by weakness, fatigability, muscular atrophy and weight loss. Muscular weakness may be generalized or may begin in a certain muscle group and later spread It does not progress to complete paralysis, though the patient may become bedridden The muscle groups affected most severely are those of the shoulder and pelvic girdle, and patients have difficulty climbing stairs Bulbar weakness may occur Ophthalmoplegia is usually absent, and chronic bulbar palsy is also rare Atrophy is common, but tendon reflexes are retained Fasciculations are frequent Creatinuria is usually present Muscle weakness may precede the thyrotoxic symptoms This condition is frequently mistaken for myasthenia gravis, but the response to the Tensilon test is negative In addition, patients present the usual signs and symptoms of hyperthyroidism Tests for hyperthyroidism are positive, i.e., basal metabolic rate, protein-bound iodine, radioactive iodine (I_{131}) uptake and low blood cholesterol values Treatment of the hyperthyroidism reverses the muscular condition. Myasthenia occurring in the course of hyperthyroidism is not to be confused with this specific myopathy This will be discussed in the Chapter on Endocrines

Polymyositis, Dermatomyositis, Neuromyositis

Polymyositis is not a single entity Its diagnosis is based upon pathologic changes in the muscle, which may be caused by infection, toxins or degeneration The two major forms are acute and chronic [13] In polymyositis, only the muscle is involved, in neuromyositis, both the muscle and the nerve are involved and in dermatomyositis the skin is also involved The characteristic pathologic picture in the active form consists of fragmentation of muscle fibers and active phagocytosis of their contents by large macrophages When skin lesions are present, histologic examination shows the dermis to be edematous, with swollen and thickened collagen The small arterials show an increase in connective tissue

in the intima and adventitia. The acute form is most frequently seen in children, but may occur at any age. Fever may or may not be present. Polymorphonuclear leukocytosis may be present. The proximal muscles are more involved than the distal and are tender, swollen and weak A diffuse erythema may be present. Respiratory paralysis may lead to death When recovery occurs, residual contractures are common. The acute form of the condition is now considered to be one of the collagen diseases.

In the chronic form the pathology is different. The periphery of the muscle fibers is vacuolated and reduced to thin sarcolemmal tubes containing large numbers of shrunken nuclei. The contents of the muscle fibers are seen to be coagulated in a segmental manner, with pyknotic nuclei. Small veins within the muscles are surrounded by clumps of lymphorrhages, plasma cell histiocytes and a few mast cells Chronic polymyositis occurs most commonly in adults and is characterized by progressive weakness and fatigability of the lower limbs. The distal muscles tend to be more affected than the proximal ones and the tendon reflexes of the affected muscles are diminished or absent. Pathologically, Adams, Denny-Brown and Pearson [13] state that there is no essential difference between the chronic changes seen in some muscle fibers in chronic polymyositis, myasthenia gravis and the more rapidly progressive forms of muscular dystrophy. Thus, pathologic examination of a muscle may not differentiate these conditions

Recently, there has been some controversy concerning patients who show the typical signs and symptoms of myasthenia, usually of an ocular type, but display little or no response to Prostigmin.[36] It has been suggested that they may have polymyositis or a form of muscular dystrophy. Classification of these patients is difficult. Carmichael [37] suggests that with the passage of time, other muscles may become affected, which may lead to the proper diagnosis of myasthenia gravis Churchill-Davidson and Richardson [38] recommend the injection of decamethonium as a means of eliciting potential myasthenic weakness in muscles that are not clinically myasthenically weak It is in such cases that Tether [39] has used the curare test The Tensilon test has been helpful, but is not always definitive in the differential diagnosis. It has been the experience of most authorities in the field that clinical responsiveness to anticholinesterase drugs is never more than 90 per cent complete and may be as low as 10 to 15 per cent. When an extremity is involved, the use of the ergogram or electromyography before and after Tensilon is helpful, and when ocular motor muscles are involved, the combination of electromyography and the Tensilon test as described by Breinin [24] aids in resolving the problem

Carcinomatous Myopathy

Changes in carcinomatous myopathy have been described as polymyositis In 1948, the occurrence of neuropathy and myopathy associated with carcinoma, but unrelated to the presence of metastasis, was reported Denny-Brown [40] reported two cases of bronchial carcinoma in which there was loss of sensibility and associated ataxia In 1950, Lennox and Prichard [41] reported five cases of peripheral neuritis among 299 cases of carcinoma of the bronchus Brain et al,[42] in 1951, reported four more cases, and Henson et al,[43] in 1954, reported 19 cases of carcinomatous neuropathy and 17 cases of myopathy associated with carcinoma of the lung In the same year Heathfield and Williams [44] reported four additional cases all associated with carcinoma of the bronchus

In 1956, Eaton [1] added 11 cases, 7 of which had malignancy of the lung and showed a myasthenia-like syndrome These 11 cases all showed generalized weakness and easy fatigability, particularly of the lower extremities Knee and ankle jerks were decreased or absent On first examination there was only slight weakness of the pelvic girdle and thighs Routine electromyography gave responses which seemed to be those of myasthenia Prostigmin and Tensilon tests were all negative or equivocal for myasthenia gravis When tested with curare these patients showed the hypersensitivity seen in myasthenia Nine were female and two male, all over 50 years of age Differentiation of this condition from myasthenia was made from the following findings absence of bulbar signs, weak tendon reflexes and poor response to anticholinesterase drugs When studied with electromyography and facilitation was induced, these patients differed from a myasthenic in showing a marked increase up to twenty times the initial potential In myasthenia the facilitation potentiation is only two to three millivolts

Brain,[45] in 1958, reported 42 additional cases, 17 of which showed a defect in neuromuscular transmission He stated that myopathy may herald the onset of carcinoma but that removal of the carcinoma does not affect the neuropathologic condition.

Psychoneurosis

A neurotic individual with muscle fatigability may present symptoms

as the day goes along There may be no history of improvement after rest Sensory complaints are much more frequent than in myasthenia and there may be fixation on a symptom, which is not typical of the myasthenic.

One must be especially aware of chronic barbiturate poisoning in this group Two patients are noted that were taking 10 and 12 Seconals a day in whom chronic barbiturate intoxication induced organic weakness Complete psychiatric evaluation assists in the differential diagnosis

Occasionally, a neurotic individual will have improvement of symptoms with a Tensilon test, improvement ordinarily expected only from a person with myasthenia gravis.[6] The use of the placebo test helps to clarify this situation. To remove all doubt it may even be necessary to give the patient a therapeutic trial with Prostigmin, Mestinon or Mytelase. Placebo tablets may be used to compare results An additional aid is the presence of an eye-closure phenomenon exhibited by some neurotics tested with Tensilon. This response is an involuntary, forcible closure of the eyelids and is often accompanied by marked muscarinic side-reactions. It should be noted that the eye-closure phenomenon could exist in the neurotic myasthenic, and its presence must be evaluated on the basis of the overall clinical findings

Undoubtedly, other general medical and neurologic disorders in rare instances may enter into the differential diagnosis of myasthenia gravis For the most part, however, we are not confronted with problems other than those noted herein. It must be emphasized again that simple awareness of myasthenia gravis in conjunction with an accurate clinical history facilitates diagnosis The combination of muscular weakness made worse by repetitive muscle contraction and improved by rest or by administration of specific anticholinesterase drugs such as Tensilon or Prostigmin is characteristic only of myasthenia gravis.

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CHAPTER VII

Specific Drug Treatment

IN TREATING the myasthenic patient, the most important concerns are early diagnosis and treatment tailored to fit the individual. Drugs used are anticholinesterases They reduce the activity of acetylcholinesterase, thereby decreasing the destruction of acetylcholine and thus reducing the block at the neuromuscular junction.

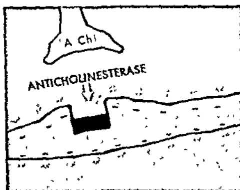


Fig 49 Schematic drawing showing action of anticholinesterase drugs at the neuromuscular junction

There are three drugs currently used in treatment. Prostigmin, Mestinon and Mytelase. As previously stated (Chapter VI), they greatly help to correct the defect at the neuromuscular junction, but they do not improve the patient to the extent attainable in a spontaneous remission The dosage of each of these drugs varies markedly from one individual to another and may change from time to time in the same patient. Control of this variation will be discussed in Chapter VIII

CURRENT DRUG THERAPY

Prostigmin (Neostigmine)

Prostigmin (neostigmine) is a dimethylcarbamic ester of 3-hydroxyphenyltrimethylammonium bromide Since its introduction over twenty years

ago the entire prognosis for this disorder has changed.[1,2,3] The drug is n habit-forming since tolerance diminishes as patients go into remissio Neither normal individuals nor patients with any other disease can tak Prostigmin in anything except small doses[4] Prostigmin is said to hav both an anticholinesterase and an anticurare action at the neuromuscula junction[5] Because of this dual action, Prostigmin has been effective i treatment of the majority of patients with this disorder, especially fo those with the milder types (Groups I and II) for whom relatively smal doses of medication are necessary.

In the more severe types (Groups III, IV and V) of myasthenia, Prostig min has distinct disadvantages because of its short duration of action Because of the increased amounts and frequency of dosage, cholinergi side-effects, such as epigastric distress, sweating, salivation, lacrimation, nausea, abdominal cramps and diarrhea become pronounced and at times difficult to control despite the use of atropine Muscle fasciculations may occur.

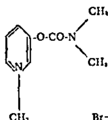
From as little as one-half of a 15 mg. tablet of Prostigmin bromide three times a day in mild cases to over 100 tablets per day in severe cases may be needed Many factors such as menstrual periods, pregnancy, infection or emotional stress can alter the daily requirement Each patient with the help of his physician must learn to adjust the dose of medicine to his immediate needs This adjustment is based both on the degree of relief of myasthenic symptoms and upon the appearance of side-reactions which indicate that an overdosage is being approached that may give rise to cholinergic reactions. The dosage of any anticholinesterase drug should be increased only slowly.

When the patient cannot swallow, Prostigmin may be given parenterally An intravenous dose of 0 5 mg is equivalent to 1 5 mg intramuscularly or 15 mg (1 tablet) orally

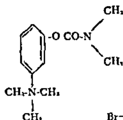
Timespan Tablets In recent years new dosage forms of various drugs have been devised that permit slow release of the medication over a longer period of time The testing in clinics of tablets of Prostigmin specially designed to maintain a slow and prolonged release of the drug has been carried out. Timespan tablets of 22 5 and 45 mg were used About one-third of the drug is released for immediate therapy, giving the effect of one-half or a whole regular tablet dose The remaining drug is released slowly. Schwab, Osserman and Tether,[6] testing these Timespan tablets, tried them in a total of 85 patients, of whom 54 found them to be of such value that they wished to continue using them The duration of effectiveness varied from a minimum of three hours to a maximum of twelve hours, averaging six to seven hours In some patients the total amount of drug taken exceeded that taken in dosages of the regular

tablets by 33 per cent without evidence either of overdosage or of better control In such cases, some portion of the dosage may escape absorption for reasons that are not clear Occasionally, the large size of the tablet bothers patients with dysphagia The greatest value of the Timespan tablet is in eliminating the need for medication during the sleeping hours. It is hoped that this dosage form of the drug will be available commercially in the near future.

A most important disadvantage of Prostigmin is that resistance to it may develop in severe myasthenia so that even increased dosages cannot completely reverse the marked weakness of the patient and may perhaps lead to cholinergic crises.



Mestinon bromide



Prostigmin bromide

Mestinon

In the past few years many new anticholinesterase drugs have become available for research in the treatment of myasthenia gravis One of these, Mestinon (R) bromide[6] (pyridostigmine bromide), which is a dimethyl carbamate of 3-hydroxy-1-methylpyridinium bromide, has been used and reported on by clinics throughout the world Unpublished observations of Randall and Lehmann[7] indicate that Mestinon has about one-sixth the acute toxicity of Prostigmin in mice by the intravenous, subcutaneous,

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The

anticholinesterase activity on purified eel esterase is about one-hundredth that of Prostigmin Studies of Blaschko, Bulbring and Chou[8] indicate that Mestinon has one-twentieth the anticurare activity of Prostigmin on phrenic-diaphragm preparations of the rat and about one-tenth of the anticholinesterase activity of Prostigmin on serum and red cell cholines-

terase. At the present time, many hundreds of patients have received this drug.

In evaluating any drug therapy for myasthenia gravis, the following criteria should be considered. (1) What is the duration of action of the drug? (2) What relief of myasthenic symptoms does it afford? (3) Is the drug relatively nontoxic? (4) Can the drug be helpful when the patient is resistant to Prostigmin?

Reports from Europe and from the major centers in this country show that Mestinon fulfills most of these requirements[9,20] The technique of serial Tensilon testing[10] was used to secure a quantitative comparison between Mestinon and Prostigmin in the same subject. Patients were stabilized on the most effective dose of Prostigmin and serial Tensilon tests were performed at hourly intervals The width of the palpebral fissures was measured Dynamometer readings were made. Any improvement in extraocular movement was recorded. Changes in diplopia, dysarthria, dysphagia and general muscle weakness were estimated Attention was paid to side-reactions such as abdominal cramps, epigastric distress, diarrhea, and skeletal muscle cramps. The need for atropine to control the muscarinic side-reactions of Prostigmin was noted. Subsequently, these patients were given Mestinon and the entire examination was repeated, with the same technique being used

The duration of action of Mestinon is slightly longer than that of Prostigmin, approximately one-half hour. However, many patients, particularly those in the group with severe symptoms, were most gratified in that they could arise in the morning without severe myasthenic symptoms. This was particularly important to those patients who, on Prostigmin therapy, could not swallow the first morning dose because of dysphagia and therefore had to receive an injection of Prostigmin methylsulfate to start the day This nocturnal relief with Mestinon has become increasingly apparent with further transfer of patients to the drug Mestinon is rarely needed during the sleeping hours.

Mestinon gives marked relief from myasthenic symptoms. It is more effective than Prostigmin in the relief of myasthenia affecting the small muscles innervated by the cranial nerves.[9] Particular relief has been noted in the muscles involved in ptosis, diplopia, and dysarthria. A few patients commented that they did not get the "lift" that they obtained from Prostigmin However, most of the patients receiving Mestinon were satisfied with the general feeling of well-being, which persisted throughout the day. Various clinics report up to 70 to 75 per cent increased clinical improvement as compared to Prostigmin.[10-14]

An example of an excellent result is the case of a man, aged 46, with manifestations of severe myasthenia gravis, with a malignant thymoma

which had been excised He had been treated with Prostigmin, 30 mg every two hours, for two years without being fully controlled in the last six months He had to be helped in walking, could not go to the bathroom by himself, and spent most of the day lying or sitting in bed His speech was slurred and ocular movement was limited both on upward and lateral gaze He was unable to raise his arms Side-reactions, including diarrhea and abdominal and skeletal muscle cramps, were present These were largely counteracted by the use of atropine, but he felt that the use of atropine further reduced the effectiveness of Prostigmin Prostigmin was withdrawn and the patient was given 120 mg of Mestinon every two hours Approximately 24 hours later he ate breakfast, got out of bed, and walked about the ward without assistance In fact, he made his own bed, which he had been unable to do for months Long-standing bilateral ptosis disappeared and there was a full range of ocular movement His limbs were strong and he lifted weights He had no side-reactions from the use of Mestinon.

For purposes of estimating the effectiveness of Mestinon, the severity of myasthenia gravis in a patient was graded on the basis of his economic usefulness to the community Severe cases were considered to be those patients so affected by myasthenia gravis that, despite therapy, they were bedridden or so weakened that they were unable to work, moderate cases were those patients who took relatively large doses of anticholinesterase medication in order to function and required frequent periods of rest during the day, and mild cases were those patients who maintained their economic place in society, were fully employable, attended school, or performed housework regardless of dosage of medication, which was usually comparatively small

A group of 81 patients before treatment with Mestinon fell into the following categories. severe, 24, moderate, 21, mild, 36 Upon transfer to Mestinon the 24 patients who were considered severely incapacitated while under treatment with Prostigmin showed such an improvement that fourteen of them could be reclassified in the moderate or mild group Of twenty-one patients who were originally in the moderate group, six were so improved that they were considered mild Forty-five per cent were improved enough to overcome their economic liability to their families and to the community

A striking advantage of Mestinon over Prostigmin is in the marked reduction in the incidence of muscarinic side-effects. This reduction in side-reactions was so pronounced that atropine could be discontinued in 75 per cent of the patients who had taken atropine with Prostigmin

Comment was made [11] on the possibility that the early warning symptoms of overdosage might be absent and special attention would be neces-

sary to avoid cholinergic effects. No difficulty on this account has been found, however, because the usual muscarine side-reactions occur as soon as overdosage of Mestinon is reached. In fact, it is easier to avoid overdosage with Mestinon than with Prostigmin because of the wider range between therapeutic and toxic effect.[10] Of course, if there is any doubt, a Tensilon test quickly resolves the problem.

Dosage. Regular Mestinon is available as a 60 mg double-scored tablet so that dosages as small as 15 mg may be given. One 60 mg. tablet of *Mestinon is equivalent in effect to one 15 mg tablet of Prostigmin* It may generally be substituted tablet for tablet for Prostigmin and is prescribed to be taken every 3 to 4 hours in most cases. Mestinon is also available from the manufacturer in 5 ml ampoules containing 2 mg per ml for parenteral use. Whether given intravenously or intramuscularly the dose of 2 mg (1 ml) is equivalent to one 60 mg tablet of regular Mestinon.

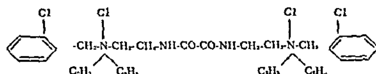
Timespan Tablets Since the myasthenic requires frequent doses of Mestinon during the daytime hours, it was suggested to the pharmaceutical concern that some form of a prolonged-action tablet be prepared. Two forms of Timespan tablets were made available· a 180 mg tablet which has the immediate effect of one 60 mg tablet of the regular Mestinon and a 90 mg tablet which has one-half the immediate effect of a regular 60 mg. tablet Schwab, Osserman and Tether[6] tried these tablets in a total of 109 patients, of which 82 found them to be of such value that they wish to continue using them, a favorable 75 per cent *The duration of effectiveness varied from a minimum of four hours to a* maximum of twelve hours, averaging approximately six hours As with Prostigmin Timespan tablets in some patients the total drug taken during the day exceeded that taken in regular tablet doses by 33 per cent without evidence either of overdosage or better control. Occasionally, patients complained of feeling weak at the time the immediately available drug would be expected to wear off, but there was a return of strength in fifteen to twenty minutes without further medication.

In general, the Timespan tablet can be expected to last about two and one-half times as long as the regular tablet. A few patients were satisfied with the action of regular Mestinon during the daytime hours and preferred taking the long-acting tablet only at bedtime. Occasionally, because of its prolonged action, it is not possible to space dosage properly over the 24 hours, so that one dose of regular Mestinon may be required in the late afternoon or early evening to fill in the hiatus between the awakening and bedtime doses.

Twenty patients used combinations of regular and prolonged-action Mestinon The largest dose of prolonged-action tablet prescribed was six tablets every six hours for a total of 24 per day; the smallest dose was one

tablet morning and night Some cases were completely controlled on a six hour basis, but later had to be reduced to a four hour schedule This new dosage form of the drug may eventually replace, to a great extent, the use of regular Mestinon.

Mytelase



Mytelase (WIN-8077)

Papers[21-26] have been published on the use of ambenonium, formerly known as Mysuran (WIN-8077) chloride This drug, now known as Mytelase, is N, N^{1}-bis (2-diethylaminoethyl) oxamide bis-2chlorobenzyl chloride. In animal experiments this drug was two to four times as active in antagonizing d-tubocurarine paralysis and the effect was of much longer duration than that of Prostigmin

Schwab[21 22] reports that of 75 patients transferred to the drug, 59 were still taking Mytelase, of which 17 were using it in combination with Prostigmin or Mestinon His patients found it preferable to Prostigmin because there were decreased side-reactions and more prolonged effectiveness.

In Westerberg's series[23] of 33 patients, 26 found Mytelase to be an effective agent in increasing muscle strength and seven found it ineffective. Thirteen patients preferred Mytelase to any anticholinesterase and continued to take it alone. Nine patients considered Mytelase equal in effect to their other medication and six of these continued to use it regularly Twelve patients had unsatisfactory results with the medication. Westerberg concludes that Mytelase is an effective drug in the treatment of myasthenia gravis and that for some patients it is the most effective therapy available Desmedt[24] treated ten patients and found the drug especially effective in the more seriously affected patient In others, he found that cholinergic intoxication occurred unless extreme precautions were observed Oftal[25] prescribed Mytelase for seven patients, all of whom refused to continue its use, either alone or in combination with Mestinon or Prostigmin. These patients did not achieve sufficient muscular strength and found that side-reactions, especially diarrhea, were severe

Eighty-two patients in The Mount Sinai Hospital series were transferred to Mytelase. The initial dose was 5 mg. or, at times, 2½ mg. and the dose was then gradually built up to therapeutic levels. In their reports Westerberg[23] and Schwab[21,22] have also cautioned about the necessity of starting with small dosages. Of the 82 patients, 23 found Mytelase superior to Mestinon and Prostigmin. Ten preferred Mytelase in combination with Mestinon. Forty-nine of our patients requested to be returned to Mestinon because of lack of relief of myasthenic symptoms.

A patient who preferred Mytelase to other drugs stated that it was the most effective drug he had taken. He can chew and swallow better with Mytelase, and although his hands tire, they are better than they were before on Mestinon.

One patient who was transferred from Mestinon to Mytelase made the following comments "(1) Mestinon gives greater strength on arising. (2) Mytelase makes the hands and legs quite a bit stronger, but seems to lose effectiveness as the day wears on (3) Mytelase and Mestinon have an equal effect on the muscles involved in speaking and eating. (4) There is not as much perspiration with Mytelase as with Mestinon. I prefer Mestinon, however, because it doesn't bother me. With Mytelase I feel as though I were falling apart."

Mytelase has a distinct advantage for the patient in crisis in a respirator since it causes less bronchial secretion than other anticholinesterase drugs This will be more fully discussed under respirator care. For the less than one per cent of patients who are sensitive to the bromide in Prostigmin and Mestinon, Mytelase chloride may be prescribed.

Mytelase is effective in the treatment of myasthenia gravis in many of the patients who have taken it. It has a prolonged action as compared to Prostigmin and possibly longer than that of Mestinon, although Grob[27] found that Mestinon was equal, if not longer, in action to Mytelase It has fewer toxic side-reactions than Prostigmin, but more than Mestinon. These side-reactions differ from those of Mestinon in that central nervous system side-reactions are more evident, particularly headaches, than with either Prostigmin or Mestinon. Although gastrointestinal side-reactions are not nearly so common as with the other two drugs, they do occur when overdosage is approached. Since they are late in appearance, muscle fasciculations and weakness are the early signs of overdosage with Mytelase. This is pointed out by Tether.[25]

Dosage. Mytelase is available in one-half scored 10 and 25 mg tablets Five to 7.5 mg of Mytelase chloride are equivalent to 15 mg. Prostigmin bromide or 60 mg. Mestinon bromide. Mytelase should be started cautiously with a 5 mg. dose and gradually increased to therapeutic levels.

It is usually given every four hours, although not during the sleeping period A syrup containing 15 mg to 5 ml. can be obtained for patients in the respirator being fed through a nasogastric tube

In regard to whether any drug can be effective when Prostigmin is not, the answer at the present time is that it is unlikely that Mestinon or Mytelase will help the patient who is resistant. There are a few cases in which Mestinon or Mytelase have been helpful because decreased side-reactions permitted higher dosages of these drugs than could be used with Prostigmin We are still searching for the drug that will be effective if the patient becomes resistant to anticholinesterase drugs.

TABLE 6. *Anticholinesterase Drug Treatment*

Original Drug

	Prostigmin	*Mestinon*
Patients	239	82

Transferred

	Mestinon	*Timespan Mestinon*	*Timespan Prostigmin*	*Mytelase*	*Combinations*
Patients	163	56	28	82	41

Current Drug

	Number of Patients	*Patient Preference*	*Current Drug* *
Remission	43	—	—
Prostigmin	46	—	17%
Timespan Prostigmin	8	30%	3%
Mestinon	144	59%	52%
Timespan Mestinon	40	70%	14%
Mytelase	23	30%	9%
Combinations	16	40%	5%

* Percentage of 320 patients using each drug

EXPERIMENTAL DRUGS

BC Drugs

From Vienna there is report of further alteration of the Prostigmin and Mestinon molecules in which polymethylene chains of various lengths, from four to ten, are attached to the carambic acid nitrogens of two rings, creating a bis form The pharmacologic character of these new substances

is changed so that they are qualitatively identical to the parent drug but are cholinesterase inhibitors of extremely strong and long-lasting action Five drugs of this type are being studied; BC-40 [29,31] (bis-Prostigmin) and BC-51 [30,31] (bis-Mestinon) are apparently the most promising These two drugs are distinguished from one another in that BC-40's action occurs more quickly but lasts a somewhat shorter time than BC-51, which develops its optimum effect only after six to twelve hours but then lasts much longer than does the effect of BC-40. Pharmacologic investigations reveal that BC-40 is about one-third and BC-51 is about one-twentieth as toxic as Prostigmin in cats. The anticurare activity of BC-51 is about one-fifth that of Prostigmin and has an equal duration of action. BC-40 is of equal potency and its duration of action is twice as long as that of Prostigmin Kraupp et al [24] reported that BC-40 was equal to Prostigmin in potency in rats but had ten times the duration of action. Both Kraupp [29] and Randall [32] report that in anticholinesterase activity, BC-40 is equal to Prostigmin in inhibiting the red cell esterase. For BC-51, Randall [32] reports an anticholinesterase activity only one-tenth as active as Prostigmin At present, we do not know if the molecules are split, or, if split, at what point They may act as a complete unit

Pateisky and his group [30] have studied the effects of the BC drugs on patients suffering from myasthenia gravis BC-40 has been given to 11 patients and 10 normal controls. The undesirable side-effects were counteracted by atropine The optimal intramuscular dose varied from 0.3 to 0.5 mg in combination with 0.5 mg. atropine sulfate. With this dose no unpleasant side-effects were noted. Twenty minutes after intramuscular injection the drug action starts and reaches its maximal effect at six hours It retains a full effect for 26 hours and then reduced doses of Prostigmin will suffice for an additional three-day period after the original injection of BC drugs. When optimal dosage is used, treatment can be given at four-day intervals The patient feels well, the appetite is increased and weight is gained.

At our clinic, we were interested in establishing oral dosage forms of the BC drugs. At first, we tried intravenous titration in an attempt to establish effective oral dosage. With BC-40 this was unsuccessful because the usual thirty-to-one ratio existing between oral and intravenous Prostigmin and Mestinon did not hold true. The ratio with BC-40 was somewhere between sixty- and one hundred-to-one, depending on the emptiness of the stomach at the time of taking BC-40. With BC-51 the ratio varied from ten- to thirty-to-one. Therefore, we discontinued this approach Five milligram, scored tablets were made available for study. Patients were started with one tablet on arising, with reduced dosage of

their previous drug continued After one to two days, a second dose of the BC drug was given at night. Gradually the BC drugs were increased, the others withdrawn until the patient was maintained on either BC-40 or BC-51 on a twice a day basis We found that these drugs are more active and have a much longer duration of action than do the parent drugs Most mild cases require no more than 15 mg twice a day and severe cases 22 5 mg twice a day. Pateisky's recommendation that these drugs be taken on an empty stomach to avoid unpredictable absorption with unevenness in control is followed.

An accumulative action similar to that of octomethylpyrophosphoramide (OMPA) (described below) caused difficulty for our group and the Johns Hopkins investigators [33] in that severe cholinergic reactions occurred on the second or third day of treatment Even with extreme care, a patient became cholinergic on the thirtieth day of treatment, the third day after an increase in the morning dose from 20 to 22 5 mg of BC-51. These drugs are still in the investigative stage, and much more information is required to determine whether they will prove to be of value in the treatment of myasthenia gravis

Oximes

Wilson et al [42,43] have studied PAM (pyridine-2-aldoxime methiodide) which has the ability to reactivate an inhibited cholinesterase enzyme, thereby giving rise to the active enzyme, with a postulated phosphorylated oxime as its final result This has been of extreme value in the overcoming of nerve-gas poisoning due to inhibition of the cholinesterase enzyme This report will certainly reopen avenues of study on the use of the alkyl phosphates in the treatment of myasthenia since one of the great difficulties in using these substances is their tremendous toxic effect [43a] DAM (diacetyl monoxime) [43b] is another oxime which has proven effective in reactivating inhibited cholinesterase enzyme Further discussion of these interesting compounds is included in the Chapter on Crisis

Discontinued Drugs

Alkyl Phosphates

In recent years potent anticholinesterase drugs, the alkyl phosphates, have been introduced for the treatment of myasthenia gravis These include di-isopropylfluorophosphate (DFP),[34] tetraethylpyrophosphate (TEPP),[31] and hexaethyltetraphosphate (HETP)[30] DFP was found to be a very effective anticholinesterase agent, but toxic and not effective thera-

peutically. HETP and TEPP were found to be more effective in treatment, but were unstable and therefore created difficulties in manufacture

In 1951, Rider et al.[37] introduced the most recent of these alkyl phosphates, octamethylpyrophosphoramide (OMPA) Gregory, Furtch and Stone[38] have compared the clinical responses of the patient with myasthenia gravis to OMPA and TEPP. Wilson et al.[39] reported on a case that did favorably with OMPA. Schulman et al[40] reported their experience with 15 cases Our experience with OMPA is described briefly below[41]

In the course of a year and a half, 12 severely ill patients were admitted to the wards for transfer to OMPA therapy in order to reduce the frequency of dosage of Prostigmin or to achieve greater smoothness of therapy[41] The daily dose of Prostigmin for each patient varied from a low of 90 mg per day to a high of 480 mg per day, averaging between 225 and 270 mg in most instances

Of 12 patients transferred to OMPA, five died. Two deaths in this group of five were due to cholinergic crisis, probably because of drug intoxication with OMPA. Two deaths occurred from malignant thymomas with metastases One death occurred in a "brittle," uncontrollable myasthenic patient who developed terminal bronchopneumonia. Six patients had to receive respirator care, these included the five mentioned above who died One other patient developed an atypical pneumonia while on the ward but recovered

Of the seven patients who are living, six discontinued OMPA therapy because of uncomfortable side-effects, despite the use of atropine sulfate, and inadequate antimyasthenic action One case developed a gastric ulcer In one case good results with OMPA were manifested by the patient's resumption of normal activities.

We conclude from our experience that the range between toxic and therapeutic dosage levels of OMPA is too narrow to warrant its continued use in the treatment of myasthenia gravis. Because of the great difficulty attendant on its manufacture, the drug was withdrawn from experimental study.

Adjuvant Drugs

Ephedrine sulfate was first used by Dr Harriet Edgeworth[44] in 1930 before the advent of Prostigmin She was a myasthenic who also had pollinosis and took ephedrine for the latter condition The ephedrine helped her myasthenia For the next few years, epedrine was the best drug for therapy, but since 1935 it has been used only as an adjunct to

treatment In this capacity ephedrine is said to increase the effect of the specific anticholinesterase drugs by about 15 per cent in many myasthenics During quantitative tests of Mestinon, ephedrine was added to the regimen, but it was found that this did not increase strength In fact, ephedrine was a great disappointment until a patient whose ptosis was unrelieved by any of the anticholinesterase drugs obtained relief from the addition of ephedrine Ephedrine is prescribed when one cannot obtain optimal results with routine therapy. If it helps the patient, it is continued If there is no better relief of myasthenic symptoms with ephedrine, it is discontinued Ephedrine sulfate is given as a 25 mg (3/8 gr) tablet three times a day

Guanidine hydrochloride was introduced in 1938 Minot, Dodd, and Riven[45] observed that it had a positive decurarizing action in the treatment of myasthenia gravis Viets and Schwab,[46] in testing 25 patients, obtained little benefit, with only four patients showing any results Later observation by Dodd et al[47] affirmed improvements, using amounts of 20 mg to 50 mg of the drug per kilogram body weight divided into three doses daily Reaction to the drug is the same as to Prostigmin in that the patient may develop an increased tolerance for guanidine, with side-reactions of gastrointestinal disturbances which can be controlled by the use of atropine

Dodd et al believe that even though patients do not get the "lift" they achieve with Prostigmin, the action of guanidine is more sustained and does not leave a sensation of weakness when it ceases There are very few further reports on this drug In our experience guanidine has been used as an adjunctive drug without any beneficial effect Only one of our patients is on a combination of Mestinon and guanidine

Potassium In 1935, Laurent and Walther[48] recommended the use of 10 to 40 gr of potassium in divided doses of 4 to 6 gr for the treatment of myasthenia gravis They stated that good results with very few side-reactions were obtained These side-reactions were diarrhea, nausea and diuresis The beneficial effect of potassium was stated by Wilson[49] to

efficacy is indisputable" As with all the adjunctive treatments, potassium has a very small role in the therapeutic armamentarium of the physician treating myasthenia gravis today With proper understanding and management of anticholinesterase drug dosage, it is only the rare case which is benefited by ephedrine, guanidine, potassium, etc

Urecholine has been advocated[51] for the therapy of myasthenia gravis

Its value is only that of an adjunct to treatment with any of the other anticholinesterase drugs. More information about this compound is required before full evaluation can be established.

Acetylcholine Accornero[52] reports favorably on the combination of Prostigmin and acetylcholine in the treatment of myasthenia gravis In all experiments acetylcholine is so short-acting that it is difficult to understand how this particular combination could be as effective as the author states.

Glutamic Acid. Dulce[53] reports on the use of glutamic acid in the treatment of myasthenia gravis and claims its action is on the central nervous system plus an uncertain effect on the neuromuscular system that seems to have some results for no known reason In this there is agreement: there is no reason for any value.

Glycocyamine Billig[54] reports metabolic alterations during betain and glycocyamine feeding in myasthenia gravis These are precursors of phosphocreatine He found that giving betain and glycocyamine was better than giving creatine in the diet and that it was made available slowly over a long period of time. It is highly questionable whether there is a true creatine defect in myasthenia gravis.

Contraindicated Drugs

Certain drugs are contraindicated in myasthenia gravis or should be used with caution These are listed below, and are discussed more fully in the Chapters on Associated Diseases and Endocrinology.

Drugs Contraindicated.

- Curare
- Quinine
- Quinidine
- Chloroform
- Morphine
- Ether

Drugs to be Used with Great Caution·

- ACTH
- Corticosteroids
- Thyroid Compounds
- Respiratory Depressants

Drugs to be Used in Small Doses

- Sedatives

Results of Treatment

An analysis of the results of drug treatment in The Mount Sinai Hospital series [55] is presented in Table 7.

Table 7 *Results of Treatment (Current Evaluation)*

		Per cent	
Better			
A	Complete remission	15%	62%
B	Marked clinical improvement, with reduction in anticholinesterase medication	30%	
C	Clinical improvement, but no reduction in anticholinesterase medication	17%	
No Change or Worse			
D	No improvement, but reduction in anticholinesterase medication	4%	20%
E	No change	8%	
F	Worse, either with or without increase in anticholinesterase medication	8%	
Dead			
G	Dead	18% *	18% *
			100%

* 3 per cent nonmyasthenic deaths

Results of drug therapy were also tabulated according to the economic usefulness of the patient to the community Table 8 shows that the number of employable patients increased from 76 to 171 as a consequence of successful drug therapy.

Table 8 *Results of Drug Treatment (Occupational Rehabilitation)*

	Before		*After*	
Employability	*No of Cases*	*Per cent*	*No of Cases*	*Per cent*
Full-time	98	34%	198	68% *
Part-time	110	38%	23	8%
None	83	28%	70	24% †

* Including current remissions
† Including deaths

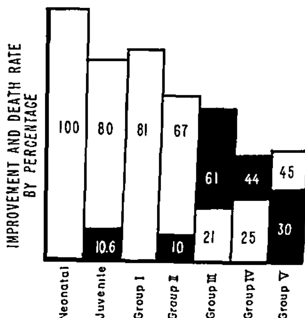


Fig 50 Improvement and death rate by clinical classification White area represents improvement and dark area represents death rate by percentage.

The bar graph in figure 50 shows that the results of treatment (evaluation key A, B and C) are excellent in the pediatric and Group I forms of myasthenia In Group II, a generalized form, two-thirds of the patients are improved. Forty-six of the 49 current remissions are in this group of patients and the death rate is very low. In the more serious forms of myasthenia (Groups III, IV, and V), clinical improvement with drug therapy is very poor, varying from 21 per cent in Group III to 45 per cent in Group V. There is a marked difference in response to drug therapy in the various groups defined in the clinical classification In general, two major categories of myasthenia are seen: the milder form, which comprises almost 75 per cent of the entire series, and the severer forms (Groups III, IV and V), in which 25 per cent of the patients are included. Of those patients who were in remission and subsequently relapsed (A'), 8 out of 30 were in Group IV or V. In these patients the death rate is very significant, varying from a high of 61 per cent in Group III to 30 per cent in Group V. We can therefore conclude that anticholinesterase drug therapy will probably control Groups I and II with the juvenile, localized, and generalized forms of myasthenia and that for the other Groups (III, IV and V), anticholinesterase drug therapy is only of partial

value Other means of treatment (see Chapters XII and XIII) may be used.

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CHAPTER VIII

Management

ONCE THE DIAGNOSIS of myasthenia gravis has been established, the management of the patient with drug therapy is begun. This is sometimes a difficult problem since the dosage requirement may vary from day to day in the same patient and, of course, varies widely from patient to patient.

Harvey [1] has raised the question of whether it would be wise to delay the use of drug therapy since he felt that with the introduction of Prostigmin bromide for treatment, the frequency of spontaneous remission has decreased. Ferguson,[2] however, has compared the remission rate of his treated patients with that of Kennedy and Moersch's series [3] of myasthenic patients followed before the use of Prostigmin and demonstrated that the remission rates in the two series are almost identical. In our series, remission rate certainly is as favorable as that in the untreated group, therefore, there is no valid reason for withholding drug treatment from the myasthenic patient. Drug therapy does relieve troublesome symptoms, including respiratory difficulty which may lead to crisis and death. Occasionally, a very mild case may be carried with minimal or no medication, but this group is so small as to be virtually nonexistent.

In the group of patients hypersensitive to anticholinesterase drugs the requirement for drugs is out of proportion in terms of symptomatology. For instance, one-fourth of a tablet of Mestinon bromide (15 mg) may make the difference between the patient having a severe cholinergic reaction and being relatively asymptomatic. Moreover, at times, these patients may have a sudden increase in need for medication to the extent of one or two additional tablets (60-120 mg.) per dose. This may be associated with infection or prodromal menstruation. Indeed, infection, menstruation in the young female, emotional trauma or excessive physical activity causes an increase in the need for anticholinesterase medication in almost any myasthenic patient.

For years dosage requirement was empirically determined. A small dose of Prostigmin was prescribed, perhaps one-half to one tablet three times a day, and the dose was gradually increased to the point of maximum relief of myasthenic symptoms. The generally accepted concept of management was that if a myasthenic patient were weak, he would be helped by increased dosages of Prostigmin. This attitude led to a belief that it would be impossible to truly overdose the myasthenic patient with Pros-

tigmin[4] True, he would get side-reactions, but these could be alleviated by the use of belladonna and its derivatives

We were impressed early in our studies, especially when using octamethyl pyrophosphoramide (OMPA) in treatment, with the fact that weakness could develop from overdosage of anticholinesterase medication Wilson[5] in 1952 pointed out the hazard of cholinergic crisis during the treatment of myasthenia gravis with OMPA Our papers published in 1953[6,7] and those of Rowland,[8] Schwab[9] and Tether[10] have emphasized the need for proper dosage This is understandable if one considers myasthenia as a metabolic disorder For instance, in another metabolic disorder, diabetes, coma can be induced by either too little or too much insulin Similarly, the problem in the management of myasthenia gravis is the selection of the most effective drug and proper dosage for the individual[11] Concisely stated, it is the administration of optimal dosage at optimal frequency

Drug Therapy

There are three important factors in drug therapy to be considered when regulating the dose for the newly diagnosed myasthenic patient or for a known patient who is not adequately controlled on current medication (1) choice of drug, (2) optimal dosage of drug, (3) frequency of administration

Choice of Drug

It is difficult to determine which of the various drugs currently used in therapy will be best for the individual patient. Mestinon bromide is recommended as the first drug to be tried in the newly diagnosed myasthenia (Chapter VII) If Mestinon does not bring about satisfactory relief of symptoms, then Prostigmin or Mytelase is tried It is best to give a therapeutic trial of one to two weeks with each drug If a single drug does not satisfactorily relieve symptoms, combinations of drugs may be used

Optimal Dosage of Drugs

Three ways to determine the optimal dosage of the drug selected are· (1) Empiric use of clinical judgment (2) Use of the Tensilon test. (3) Use of intravenous titration, with extreme caution because of the *serious hazards* involved in the procedure.

Empiric Method The patient is given an arbitrary dose of an anticholinesterase drug, usually one tablet three times a day The patient is asked to observe the degree of relief of symptoms he attains on this dose. Each patient finds for himself some particular indicator which he uses as

a sign of the need for medication. This is not necessarily a typical physical symptom or sign, although it may be, but, rather, is a feeling which heralds the onset of such symptoms or signs Examples of such an indicator are stiffness of the tongue, stiffness of the gums, dryness of the mouth, haziness of vision, puckering of the lips, paresthesias, etc. It is important to discuss this factor with each patient and to use this type of signal of onset of weakness in judging by the empiric method With a patient new to myasthenia, it will take a while for him to recognize this aura mechanism.

The patient is also alerted to muscarinic (cholinergic) side-reactions such as sweating, salivation, tearing of eyes, epigastric cramps and diarrhea and is told to report to the physician by phone. If the side-reactions are prominent, the dosage is too high and he is asked to reduce the dose. If there is no relief or insufficient relief of myasthenic symptoms from one tablet, the dose is increased by one-half or one tablet. This continues until maximal effect is obtained

When too large a dose of anticholinesterase drug is taken, the patient notices the following (1) no relief of the myasthenic symptoms in the usual 45-minute to one-hour period following the intake of medication, (2) side-reactions are present, (3) two or three hours after the dose he begins to feel better and then weakens a few hours later This latter is because the weakness of the inherent myasthenia is replaced by an overdepolarization weakness (cholinergic reaction). Only when the excess amount of drug has left his body does he receive any benefit from the drug. Gradually, as more and more of the medicine is destroyed, he again becomes myasthenically weak

When a patient has had an insufficient amount of the drug, he feels weak continuously with perhaps a slight improvement at the normal 45-minute period (usual absorption time from the gastrointestinal tract). By training the patient to observe a time relationship between weakness and strength and the presence or absence of muscarinic side-reactions, it is possible to adjust the dosage of medication Optimal dosage results in maximum muscle strength without any or with minimal side-reactions

The relationship of the dose to meals is important since a large percentage of myasthenic patients have difficulty in chewing and swallowing. It is important that this group of patients take their medication about three-quarters of an hour before mealtime so that they will have sufficient strength to chew and swallow food This time may vary from patient to patient. When medication is taken on an empty stomach the patient may find it effective in as little time as twenty minutes Some patients complain of severe gastrointestinal reactions when anticholinesterase medication is taken on an empty stomach. Patients note that pills taken immediately

before, during or shortly after a heavy meal are somewhat less effective Problems related to mealtime seem to be more common with patients using Prostigmin than with those using Mestinon or Mytelase It is important to adjust dosage and meals to the individual

Since the symptomatology varies during the day and varies with the amount of activity of the patient, it may be necessary to vary the dosages during the day Most patients awake in relatively good strength and need less of the drug in the morning hours than they do in the afternoon On the other hand, some of the more seriously ill myasthenics need a larger dose upon arising in order to start the day, but if they continue using the same amount of drug during the day, they show signs of overdosage after the second or third dose In the evening, need for medication depends upon activity If the patient stays at home and rests, the need may be less, whereas, if he is going out, he may need a slightly increased dose The dose must be tailored to the individual patient and his changing needs In the majority of cases the same dose can be taken throughout the day, but for others there will be variations of one-half to two pills at different times of the day

Some patients are poorly controlled because they take too small a dose of medication too often For example, one patient was taking one tablet every 30 to 60 minutes, a total of 26 pills a day, with poor results When properly regulated at two and a half tablets every three hours, a total of seventeen and a half tablets a day, her strength became almost normal.

Belladonna derivatives should never be used routinely as they tend to obscure symptoms needed for information They should be used only to treat cholinergic reaction specifically Atropine sulfate in hypo tablet form, gr $\frac{1}{150}$, is prescribed for all patients so that they may either swallow or put them under the tongue if cholinergic reaction occurs

The Tensilon Test A new approach to the management of myasthenia gravis has been evolved through the use of Tensilon chloride as a testing agent[12-16] to permit the clinician to judge the effectiveness of therapy. We first used Tensilon as a rapid diagnostic test,[17] but even in our first report we noted "Several patients were retested when well controlled by medication One patient was retested while in a state of remission. These patients showed mild fasciculations The absence or presence of fasciculations is a sensitive index for the effectiveness of therapy in myasthenia gravis" Subsequently, it was noted that the response to the Tensilon test depended upon the time which had elapsed since the last dose of medication and the amount of drug taken[6,7]

The following technique using the Tensilon test[15] *for management is* recommended One hour after oral administration of the therapeutic drug, a tuberculin syringe containing 0 2 ml (2 mg) of Tensilon chloride

is prepared and is injected intravenously within 15 seconds. In adults with inaccessible veins, the dose is 1.0 ml. (10 mg) of Tensilon injected intramuscularly. For dose for children, see Chapter V. All signs that would appear with the intravenously given test also appear with the intramuscular test, except that there is a delay of two to ten minutes before a reaction takes place.

With the intravenous test several effects are observed within 30 to 60 seconds. These consist of: (1) changes in muscle strength; (2) the presence or absence of fasciculations; (3) the presence or absence of side-reactions In performing this procedure on myasthenic patients under treatment, three types of response are noted: (1) myasthenic (in the inadequately treated patient), (2) adequate (ideal state), (3) cholinergic (in the overtreated patient).

Responses to Tensilon Test *

	Myasthenic	*Adequate*	*Cholinergic*
Muscle strength	Increased	No change	Decreased
Ptosis			
Diplopia			
Dysphonia			
Dysphagia			
Dysarthria			
Respiration			
Limb Strength			
Fasciculations	Absent	Present or absent	Present or absent
Orbicularis oculi			
Facial muscles			
Limb Muscles			
Side-reactions	Absent	Minimal	Severe
Pallor			
Lacrimation			
Diaphoresis			
Salivation			
Abdominal cramps			
Nausea			
Vomiting			
Diarrhea			
Headache			

* Reprinted, by permission, from Osserman, K. E., Kaplan, L. I., and Besson, G. J. Mt Sinai Hosp 20 165, 1953, and Osserman, K. E. and Kaplan, L. I Arch Neurol & Psychiat 70 385, 1953

Figure 51 graphically portrays the use and interpretation of the Tensilon test Point A represents a patient untreated or undertreated. In this

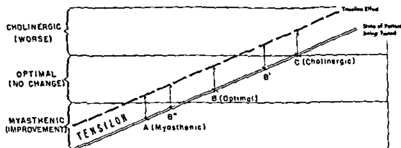


Fig 51 Tensilon in management.

case the Tensilon has an additive effect The patient is brought up to optimal or adequate dosage When improvement is obtained after the administration of Tensilon, it can be assumed that the concentration of treatment drug at the time of the test was less than optimal and that the patient is being undertreated. This is a myasthenic reaction in which there are subjective and objective findings of increased strength without fasciculations or side-reactions

At Point C the muscle function is depressed due to supra-optimal concentration of the anticholinesterase drug The additive effect of the Tensilon increases the patient's symptoms. When the Tensilon test makes the patient worse this indicates that he is taking too much drugs In order for a response to be called cholinergic, the following findings are minimal (1) the patient complains of feeling worse; (2) increased weakness is noted by the examiner; (3) side-reactions may vary from very mild to very severe and may become the dominant feature Fasciculations may be seen, but their absence does not preclude a cholinergic response if the other factors are present

At Point B the concentration of the treatment drug is at optimal or adequate levels and this slight increase in concentration induced by Tensilon does not appreciably change the patient's condition Under these circumstances the dosage of treatment drug at the time of testing is adequate or optimal This adequate response is the ideal state in treatment When Tensilon is given to a normal patient, he will show fasciculations and mild side-reactions, but no change in strength The perfectly controlled myasthenic should respond in the same manner. The range of adequate responses is wide. They may vary from the cholinergic side of adequate to the myasthenic side of adequate (points B′ and B″) The response may show some features of both extremes Muscarinic effects may predominate on the cholinergic side and be evidenced by lacrimation

or salivation, while the nicotinic effects may occur on the myasthenic side as evidenced by an equivocal increase in ability to swallow or an equivocal decrease in ptosis. The important single feature of the adequate response, however, is that any change noted, be it in strength, side-reactions, or fasciculations, is a very mild one. It has been found that the safest and most productive rule to follow is that if no myasthenic response is elicited with the Tensilon test, i e, marked improvement, no increase in anticholinesterase medication should be given.

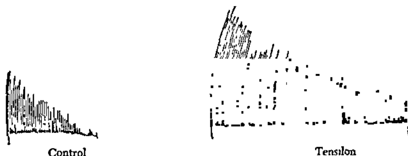


Fig 52 Erogram showing myasthenic reaction.



Fig 53 Erogram showing optimal or adequate response.

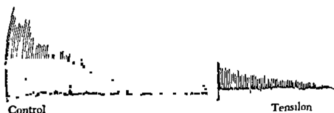


Fig 54 Cholinergic reaction ergographically illustrated, point C.

Titration In an attempt to attain proper dosage at the first visit, a method of *intravenous titration* with anticholinesterase treatment drug was developed. This method depends upon a conversion table which is most useful (Table 9).

TABLE 9

Drug	Intravenous	Intramuscular	Oral
Prostigmin bromide			15 mg
Prostigmin methylsulfate	0 5 mg	1 5 mg	
Mestinon bromide	2 0 mg	2 0 mg	60 mg
Mytelase chloride	?	?	5-7 5 mg

As seen in table 9, the intravenous and the intramuscular dosage of Prostigmin differ, whereas the intravenous and intramuscular dosage of Mestinon are the same Advantage was taken of this and an intravenous solution containing 2 mg of Mestinon bromide per ml was made available for clinical investigation At the first visit, when the patient is in his most severe myasthenic state, (basal state without anticholinesterase medication), a Tensilon test is performed with or without mechanical aids and the diagnosis is established After five to ten minutes, the patient will return to his myasthenic state At this point, the patient is re-evaluated and certain outstanding symptoms are used as a criteria for improvement For instance, ptosis, dysphonia, diplopia or weakness of the neck muscles may be used alone Limb weakness can be judged clinically or by the use of the hand dynamometer A more accurate evaluation would be made by five or six strokes performed on the ergogram Difficulty in swallowing may be judged with the aid of barium and the fluoroscope Diplopia can be measured clinically or with the use of the red glass test

Certain very important cautions must be observed in the technique of titration

1 If anticholinesterase drugs are given rapidly or in large amounts, severe cholinergic reaction and even death may ensue Strict attention must be paid to the patient and if he complains of stomach cramps or abdominal queasiness, *the titration must be discontinued immediately*

2 *A syringe with 1 mg of intravenous atropine sulfate must* always be prepared before titration is begun If ever in doubt, give 1 mg of atropine intravenously (2 5 ml of stock vial of atropine sulfate containing $\frac{1}{150}$ grain per ml) Atropine cannot possibly hurt the patient and may prevent a good deal of trouble

3 *The titration must be stopped* when maximum improvement in any one sign is achieved This is emphasized because a myasthenic patient most frequently has more than one physical sign For example, if ptosis is completely relieved but limb weakness remains and more anticholinesterase drug is injected in an attempt to correct the limb weakness, ptosis due to toxicity (cholinergic reaction) will develop If the drug is pushed far enough, complete cholinergic reaction will occur and collapse will follow This has been proved experimentally when with knowledge of

the hazards involved, an attempt has been made to overcome all weakness in the seriously ill myasthenic patient. Rowland et al.[3] approached the problem with a different procedure, but arrived at the same conclusions.

In the recommended *titration method*, a 5 ml. syringe is filled accurately with 10 mg. of Mestinon bromide. The needle is inserted into the vein and only one drop of blood is drawn back into the syringe. The examiner must be seated and comfortable so that he will not unconsciously rush the titration since it usually takes 10 to 15 minutes or more to complete the procedure. A stop watch should be placed so that the examiner can easily watch the time. It is important that the plunger and the barrel be kept at constant level with each other to prevent a backflow of blood into the syringe or further injection of Mestinon into the vein

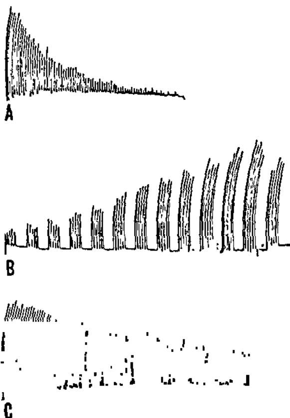


Fig 55 Erogram *A*, before medication *B*, with increments of 0 25 ml. Mestinon bromide each minute, showing best effort at 2 75 ml and a fall-off at 3 ml. (6 mg). *C*, ergogram five minutes after titration.

At this point, the muscle strength is evaluated and ¼ ml of solution is injected into the vein. After a wait of one minute (in some patients with slow reactions, two minutes), the patient is re-evaluated. This continues at one-minute intervals with increments of ¼ ml until the patient subjectively and the examiner objectively, both clinically and by observing the results of mechanical tests, agree that a good result has been attained. It is advisable to give ¼ ml more to ascertain that peak results were obtained with the previous dose. At this point the patient will probably

come these side-effects.

At the end of the titration the intravenous dose at the point of maximum effect is converted to the oral dose by the use of the conversion table. If 3 mg. or 1.5 ml of intravenous Mestinon bromide was required for maximum effect, the patient may be given an initial dose of 90 mg (1½ tablet) of Mestinon bromide or 22.5 mg. (1½ tablet) of Prostigmin bromide. The conversion factors for Mytelase have not been accurately determined, but the probable dosage would be 7.5 mg. Experience has shown that it is best not to convert from the intravenous Mestinon dose to an oral Mytelase dose. To establish proper dosage of Mytelase an empiric oral dose is given followed by a Tensilon test one hour later. The usual first dose is 5 mg. of Mytelase.

Frequency of Dosage

Optimal frequency is the administration of adequate doses at such time intervals as will maintain continuous optimal effect.

Empiric. Proper frequency of dosage can best be determined clinically by observing when effects begin to wear off. The timing is based on the patient's subjective and the physician's objective findings regarding the duration of the action of the drug.

Tensilon Test. The following procedure is recommended: The patient in a basal state is given his dose of treatment drug and Tensilon tests are performed on an *hourly* basis, until the medication has exhausted its action and the patient shows a definite myasthenic response. At this point the elapsed time designates the frequency with which the drug should be administered.

In evaluating and comparing new drug therapies the Tensilon test is a valuable tool. It helps to determine the duration of activity of the medication.

If the patient is not controlled, changes in drug dosage can be ordered, an increase if the Tensilon response was myasthenic at one hour post-

medication, a decrease if the Tensilon response was cholinergic. If the response is optimal but the patient is not well controlled clinically, the drug should be changed. If the weakness is greatest in the extremities, Prostigmin or Mytelase may be tried. If the weakness is mostly of a bulbar nature, Mestinon or Mytelase may be tried. If at subsequent visits the single drug does not give the desired effect, combinations may be used. The combination employed depends upon the area of weakness. Prostigmin and Mytelase may be best for weakness of the extremities, Mestinon and Mytelase best for bulbar weakness, Mestinon and Prostigmin best for bulbar and skeletal weakness.

Mechanical Aids

As stated before, the effectiveness of drug therapy is variable in the myasthenic patient. Most patients attain sufficient relief with drug therapy to maintain a fairly normal life. However, the effectiveness of therapy leaves much to be desired in some patients. Physiotherapy can be of great help in preventing atrophy of disuse by means of passive motion and even the encouragement of guided active motion. Prevention of foot drop and other such entities can be avoided by proper use of the modalities employed in physical medicine. For Group V patients with atrophy, varied rehabilitation measures can be prescribed which may enable the patient to lead a more normal life. The question has been raised whether exercise might not increase the need for specific drug therapy. When physiotherapy is properly administered, patients do not require any increased dosage and are physically improved.

Ptosis When ptosis is present to the extent that the lid closes over the pupil, resulting in partial loss of vision, a plastic or wire lid crutch attached to an eyeglass frame may be worn to correct the condition.

Diplopia An eye patch can be worn over one eye, thus permitting the patient single vision. The patch should be changed from one eye to the other to prevent the suppression of vision which would occur if the same eye were kept constantly covered. If only one eye is covered, further paresis of extraocular muscles with atrophy of disuse may ensue The opthalmologist may prescribe prism lenses to correct the diplopia, however, the degree of prism needed varies with the patient's myasthenic condition so the problem is not completely solved by this means

Various operations have been performed to correct ptosis and diplopia In myasthenia gravis surgery is not justified since the patient's condition changes with time and the surgical procedures may prove to be a handicap

Difficulty in Chewing Since it is difficult to feed these patients a well-

balanced diet, a homogenizer is useful in preparing the food so that the patient can swallow it with a minimum of effort

Dysphagia If dysphagia becomes a persistent problem and the patient is losing weight because of insufficient alimentation, a nasogastric tube with gavage feeding is essential to maintain proper nutritional health Because the pharyngeal reflexes are weak in these patients, the tube can be passed with great ease. In fact, the patient can be taught to pass his own tube at feeding times Great care must be taken to place the tube in the stomach and not in the tracheal-bronchial tree This can be determined by placing the tip of the tube to the ear and listening for the gastric boborygmi If respiratory exchange is felt or heard, the tube is misplaced Another method is to withdraw some stomach content by means of suction with a syringe One must be most careful not to overfeed since this may cause regurgitation, with aspiration of food into the lungs

Suction A simple suction apparatus can be rented or purchased for home use for the seriously ill myasthenic who tends to develop hypersecretion in the nasopharynx with poor ability to cough The patient can be taught to use the suction appliance himself to clear saliva and mucus

Weakness of the Extremities No braces or orthopedic appliances are helpful Because the weakness is usually fairly well generalized in all extremities, it is difficult to place the burden of one extremity upon another by mechanical means A cane may be very useful, however, for the patient with limb weakness, particularly with atrophy of the lower extremities.

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CHAPTER IX

Crisis

SUDDEN, UNEXPLAINED DEATH is still not rare in myasthenia gravis. Most patients who succumb pass through a phase in which they are unable to maintain proper pulmonary ventilation despite increasingly large doses of anticholinesterase medication This is due to weakness of the respiratory muscles, including the diaphragm and the intercostal muscles, and obstruction of the airway from weakness of the laryngeal and pharyngeal muscles, which frequently results in atalectasis and pneumonia from the inability to cough up secretions.

In 1953, we pointed out that the patient with myasthenia gravis may develop weakness either as an inherent part of the disease or from overtreatment with anticholinesterase drugs [1] The differentiation of these two types of weakness presents a difficult and serious problem, often unrecognized in the management of the patient with myasthenia gravis. The rapidity of onset of weakness which may lead to fatal termination justifies use of the terms "myasthenic crisis" and "cholinergic crisis," the latter being appropriate when the weakness is due to overtreatment with anticholinesterase medication

For many years it was not properly recognized that overdosage with anticholinesterase drugs could induce a crisis in a myasthenic patient. Since the advent of a number of organic esters of phosphoric acid derivatives for treatment of this disease, cholinergic crises have become more frequent In 1952, Wilson, Williams and Miller [2] pointed out the hazards of cholinergic crisis in the treatment of myasthenia gravis with octomethylpyrophosphoramide (OMPA). Although it was known that this drug could create overdosage symptoms, as was pointed out by Schulman, Rider and Richter,[3] and others working with the phosphorylated compounds,[4,5,6] the effect of the quaternary ammonium salts was said not to create much distress except for muscarinic side-reactions It was felt that a myasthenic could always increase the dose of anticholinesterase medication in order to obtain better results

Randt [7] stated that a myasthenic crisis "may indeed be precipitated or contributed to by overdosage with Prostigmin which is known to have a curarizing effect, producing directly opposite results in the patient from those desired to maintain life" It is possible that many patients previously thought to be in crisis due to drug resistance were actually in cholinergic crisis We reported that myasthenic and cholinergic weakness did occur

in the same patient and that the latter was due to overdosage with Prostigmin [8]

Rowland et al [9] concluded from an experiment that Prostigmin administered in large amounts intravenously could cause significant weakness in patients with myasthenia gravis, that the Prostigmin-induced weakness was usually preceded by improvement in clinically weak muscles, but that the improvement was usually incomplete. In one patient large amounts of the drug failed to invoke any improvement before eliciting weakness. The pattern of weakness was not consistent, but muscles which had not been clinically weak previously were usually affected simultaneously with myasthenic muscles. Subsequently, more and more reports have appeared in the literature [10-13]

The pathophysiology of myasthenic crisis is the same as that of myasthenia gravis During crisis, due to some factor which as yet is not thoroughly understood, anticholinesterase drugs do not overcome the block at the neuromuscular junction Churchill-Davidson and Richardson [14] hypothesize an altered response at the neuromuscular junction. Myasthenic crisis most frequently occurs in association with upper respiratory infection or with emotional or physical trauma A clue to the possible mechanism might be in the work on blood complement levels by Nastuk et al.[15] which shows that the blood complement level is markedly decreased, at times to zero, with the onset of crisis It does not explain why the patient becomes increasingly resistant to anticholinesterase medication, even to the point of complete unresponsiveness. When increasing amounts of anticholinesterase medication are given to these patients in an attempt to overcome the curare-like block, these drugs cause an entirely different type of block, namely, an overdepolarization block which in turn leads to further weakness and the condition known as cholinergic crisis.

The major effect of anticholinesterase drugs, as pointed out in the Chapter on Physiology, is to increase the action of acetylcholine at the neuromuscular junction. It has long been known that the action of acetylcholine is twofold [16] a muscarine-like action on smooth muscles and glands and a nicotine-like action on ganglia and striated muscle The nicotine-like action is also a twofold one: in small doses it is manifested by stimulation of neuromuscular activity, in large doses it is manifested by depression of this activity, and even paralysis. It is well known that the myasthenic patient can tolerate much larger doses of acetylcholine and other anticholinesterase drugs than the normal person This does not eliminate the

cular depolarizing block (nicotine-like effect) which causes increased weakness, and ultimately paralysis, of muscle (cholinergic crisis)

The clinical syndrome of cholinergic crisis is best seen in those non-myasthenic patients who have been exposed to anticholinesterase insecticides Such cases were first reported by Grob and his associates.[17] The patient is extremely weak, often becomes comatose in a short time, and has respiratory difficulty. In a review, Grob added to this knowledge of

sist of anorexia, nausea, sweating, and epigastric and substernal tightness, with heartburn and eructation These initial effects are followed by abdominal cramps, increased peristalsis, vomiting, profuse sweating, and dyspnea, with reduction in vital capacity and in maximal breathing capacity.

2 Nicotine-like effects Shortly after the onset of the moderate, muscarine-like effects, increased fatigability, mild generalized weakness, involuntary muscular twitchings, scattered fasciculations, and sometimes muscle cramps ensue Extensive exposure results in severe generalized

graphic studies show alterations in neuromuscular function which are attributable to the accumulation of excessive acetylcholine at the motor end-plate

3 Effects on the central nervous system. These include tension, anxiety, extreme nervousness, restlessness, emotional lability, and giddiness. Later, insomnia, with excessive dreaming and occasional nightmares, occurs. If exposure is extensive, headache, tremor, drowsiness, difficulty in concentration, slowness of recall and mental confusion develop Severe exposure to Parathion (p-nitrophenyl diethylthionophosphate, an insecticide) causes ataxia, slurring of speech, coma, areflexia, Cheyne-Stokes respiration, generalized convulsions, and, finally, depression of respiration

Differentiation of Myasthenic and Cholinergic Crisis

This problem has been succinctly summed up by the editor of the 1956-1957 Yearbook of Neurology and Psychiatry: "The dilemma between myasthenic and cholinergic crises is desperate General statements such as those of Rowland et al.[10]—'in critical situations, there is greater likelihood of administering too little rather than too much medication'—and of Tether[14]—'when adequacy of dosage is doubted, it is better to underdose

than to overdose'—contradict each other and are dangerous guides. Close attention to clinical signs of muscarine intoxication is paramount and testing with Tensilon most helpful."[20]

Too frequently when a patient develops respiratory distress there is a tendency to give specific anticholinesterase drugs in an attempt to relieve the symptomatology If the difficulty is myasthenic, no damage is done *with this therapy. In fact, the patient may be markedly improved even* though the relief is temporary. If the condition is due to overdosage, real harm can result from the use of anticholinesterase medication. This is comparable to the problem of coma in the diabetic. In diabetic coma insulin is indicated, however, in hypoglycemic coma, insulin is markedly contraindicated

If the patient is able to give a history, the relationship of time and dosage is most important in making the differential diagnosis. The patient in myasthenic crisis will give a history of an intervening infection, emotional trauma, perhaps a relationship to the menstrual cycle, or cessation of medication The usual dose of drug becomes ineffective, but there is no history of increased weakness or side-reactions *after* taking medication

The history of cholinergic crisis may begin in much the same way, however, the patient then keeps increasing the amount and frequency of medication with less and less effect and with supervening side-reactions, particularly those associated with the secretion of glands and the gastrointestinal tract. Less frequently, cholinergic crisis occurs when a patient who has been taking relatively large amounts of drug to control myasthenic symptoms starts into a remission His drug at that point causes weakness, but the patient increases the dosage, instead of reducing it In one case the patient had increased his dosage to eight tablets of Prostigmin every hour He barely managed to get to the doctor's office. All medication was withdrawn and five hours later the patient began to feel normal Later, Tensilon tests showed that the patient was in a remission and all medication was stopped

The patient in cholinergic crisis presents on examination the same marked weakness seen in myasthenic crisis, but there is generally an evident pallor, a marked tendency to hypertension, bradycardia, myosis of the pupils, excessive salivation, marked perspiration, muscular fasciculation and the skin is cold and clammy. With this rather distinctive clinical picture, it would seem that if a little time were taken, there should be no difficulty with clinical differentiation.

Tether[13] has pointed out that sometimes patients will swing from one type of weakness to the other without presenting all the classical features. He stated that cholinergic reaction may occur so suddenly that muscarinic symptoms and even fasciculations may be absent. The paralysis of the

muscles of deglutition and respiration may occur so rapidly that the condition will resemble myasthenic crisis and the desperate patient or physician will add even more anticholinesterase drug, with disastrous results. In this situation the Tensilon test is most valuable in differentiating cholinergic or myasthenic weakness.

Tensilon Test in Crises

Now recommended[21] is 0.1 ml (1 mg) or, at the most, 0.2 ml (2 mg.) of Tensilon for intravenous testing dose In crisis there are only two responses to the Tensilon test which are significant. Only if the patient is markedly improved by the Tensilon test do we consider the response to be myasthenic. Any other response to the test, whether equivocal or an exacerbation of symptoms, we consider to be cholinergic Using the Tensilon test in this way, it is an invaluable guide in the management of the patient in crisis

The following table analyzes crises that occurred at The Mount Sinai Hospital Fifty-seven patients, an incidence of 17.5 per cent, had a total of 67 crises, 47 were myasthenic crises and 20 were cholinergic Some of these were mixed crises in which the patient swung from one type to the other Fifty-one of the crises were treated with respirator care and 31 of the respirator cases were tracheostomized

	Number of Patients
Myasthenic Crises	47
Cholinergic Crises	20
Respirator Care	51
Tracheostomy	31

Treatment of Crisis

Coordinated teamwork is essential in the emergency case since various medical disciplines are required in the treatment of crisis. The otolaryngologist must be prepared for emergency bronchoscopy and tracheostomy The anesthetist must be available for laryngeal intubation and institution of bag-breathing during tracheostomy The resident staff must be thoroughly trained and alert since timing is most important in the care of these patients Above all, excellent nursing care is mandatory. The physician, be he a general practitioner, internist or neurologist, bears the responsibility of directing treatment and coordinating the various members of the team

Drug Therapy

In crisis the most important factor is the maintenance of adequate respiratory exchange. The use of drug therapy is the first step If the crisis

is myasthenic, anticholinesterase drugs can be given orally or parenterally if the patient is unable to swallow. In this condition, intravenous titration as described in the Chapter on Management can be extremely helpful. As in diabetic acidosis, the patient is resistant and needs some increase in dosage. Extreme caution is required in the use of this technique. We have seen a dosage of 20 mg. of injectable Mestinon become ineffective within one-half to three-quarters of an hour. When such resistance occurs, it is not advisable to keep administering anticholinesterase medication since the patient may be thrown from a myasthenic crisis into a more serious cholinergic crisis. Some patients have been maintained through myasthenic crisis by intravenous Mestinon titration, avoiding the use of the respirator with the attendant difficulties for the patient and the nursing and house staff

When the diagnosis is cholinergic crisis, atropine sulfate in large dosage is administered.[22] Grob [18] has pointed out that it is practically impossible to do damage with atropine. An initial injection of 1 mg. atropine, intravenous or subcutaneous, is recommended. If this does not control the crisis quickly, mechanical means of maintaining respiration should be used immediately. In one case of severe cholinergic coma in which the patient was immediately placed in a respirator, 8 mg atropine was given in the first four hours of treatment This controlled the severe side-reactions When the pupils became slightly dilated, further atropine was discontinued Fourteen hours later, a Tensilon test showed a myasthenic response in that respiration was improved by the test Nevertheless, the patient never recovered from the coma and died 20 hours later. This is again comparable to the diabetic coma in which all the chemistries are returned to normal, yet the patient expires in coma because of irreparable damage to the brain

Perhaps the most important point regarding drug treatment in crisis is that it is best to treat the patient for cholinergic crisis by giving atropine if any uncertainty exists regarding the nature of the crisis If this gives no relief, the patient should be given artificial respiration and then placed in a respirator.

Most encouraging reports by Grob,[23 25] which may well resolve the therapeutic problem of cholinergic crisis in the future, deal with the intravenous administration of PAM (pyridine-2-aldoxime methiodide) or DAM (diacetyl monoxime), which were briefly discussed in the Chapter on Drug Treatment. He has found that these drugs reverse the cholinergic effect of the quaternary ammonium compounds (Prostigmin, Mestinon, Mytelase, BC-40 and BC-51). PAM and DAM have no effect on the muscarinic side-reactions, which still require the administration of atropine. To overcome nicotinic effects, he recommends a slow intravenous titration with either PAM or DAM, starting with 2 grams in the syringe.

He injects 0 5 grams at the rate of 10 mg. per second He recommends a five to ten minute wait before administering additional 0 5 gram doses The titration is stopped when strength is restored to optimal level Usually 1 0 to 1 5 grams are necessary. DAM has a tendency to create a burning sensation at the site of injection Grob has suggested that the aldoxime may be used as the antithesis of the Tensilon test in differentiating the two types of crisis.

Respirator Care

If breathing stops, adequate air exchange *must* be achieved within *five* minutes As in other medical emergencies, irreversible changes take place in the brain after anoxia has lasted for longer than this.

A stand-by respirator must be available just outside the room or ward in any severe case of myasthenia with any signs of dyspnea. The respirator should be carefully checked to insure its usability, extra fuses should be maintained at the fuse box, the location of which should be determined. In case of power failure, a handle at the bellows permits manual operation of the respirator A gasoline generator is available for patients who must be transported.

When a patient with dyspnea is at home, a member of the family should be taught to perform artificial respiration so that if the patient stops breathing, no time will be lost while waiting for an ambulance

Once the patient is placed in the respirator, an unobstructed airway must [illegible]
bec [illegible]
the [illegible]
ing out the oropharynx and a small catheter is used through the nose into the nasopharynx Suction should be performed frequently, as often as every five minutes If the secretion seems to thicken and the patient develops cyanosis, bronchoscopy is a life-saving procedure The bronchoscope may be passed through the tracheostomy if present and plugs of mucus suctioned out Percussion and auscultation with the machine turned off may reveal massive atalectasis, which can be relieved only through bronchoscopy with suction An emergency tracheostomy set and an emergency bronchoscopy set must be kept in the room of the respirator patient.

Atropine is discontinued when the patient is in a respirator Although it may dry up excessive secretion, it has a tendency to cause inspissation, which makes the secretion difficult to remove by suction.

Negative Pressure Respirators

The negative pressure respirator has two main portals a stationary oval tube with a rubber diaphragm at the end which can be moved back

and forth by the motor to create changes in pressure. Into this is inserted the movable bed with a headpiece which can be hermetically sealed when the parts are telescoped together. In the headpiece is a collar through which the patient's head can be passed. Two types of collars are available. The plastic collar has a spring which can be tightened around the patient's neck. The thick sponge-rubber collar has five straps placed from the inside which have various notches to adjust the collar around the patient's neck. These straps are attached to pegs on the outside of the respirator.

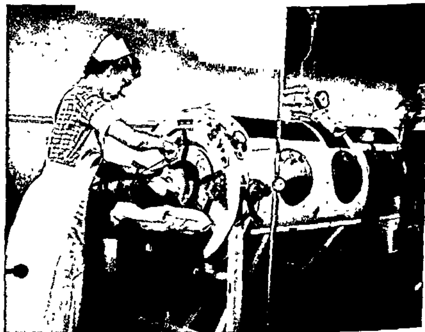


Fig 56 Patient in a respirator

In placing the patient in the respirator, the two parts are separated and the collar opened as wide as possible. The patient is then placed on the bed and the head is drawn out through the open collar. A soft towel is placed around the neck and comes down over the chest in an X-shaped form. The straps are then released and the collar is fitted snugly around the neck. The bed part is then pushed into the stationary part and the head sealed by using the clamps on either side of the respirator. There are two switches at the foot end of the stationary part. One turns the light on in the respirator and the other turns on the motor. There are

three portholes with sponge rubber protection on one side of the stationary part. The other side has two portholes and one larger one without a rubber protection which is used to pass in a bedpan. The other portholes are used either by the physician or the nurse, the rubber making a seal over the hands so that negative pressure is maintained.

The machine is then turned on and the gauge on top is observed for the amount of pressure. A knob near the switches can be used for the regulation of negative pressure. At the dorsal end of the static tank is a flap with a screw which is used to develop positive pressure. A fly wheel near the floor regulates the speed of respirations. A temperature gauge is set within the respirator so that atmosphere temperature can be observed. A jack, movable by hydrolic pressure, allows the patient to be put into a Trendelenburg position. Near the head of the respirator are two wheels which tilt the bed from one side to the other.

We prefer the sponge rubber collar, but at times it must be properly padded with gauze pads to maintain a true hermetic seal. The machine is adjusted to a negative pressure of -15 to -18, usually with no positive pressure, or perhaps only $+2$ or $+3$. The rate of respiration is set at a low figure, twelve to fourteen per minute. The patient naturally would feel better with higher negative pressure (-20 to -25), but this makes it difficult later to wean the patient from the respirator. The rate of respiration is kept low because this also allows a better exchange of gases. When the respirator runs at the normal rate of respiration, i.e., 20 per minute, there is not a sufficient exchange of alveolar gases, with a tendency to blow off the CO_2 resulting in alkalosis.

Proptosis tends to develop when the patient is placed in the respirator. This may be due to compression of the collar about the neck or may be a manifestation of an endocrine imbalance. A tendency for complete ophthalmoplegia to develop in the patient in myasthenic crisis is noted. Eye care is essential. The lids should be kept shut, by taping if necessary.

While the patient is in the respirator and aphonic, he may be given a magic slate such as children use as toys so that he can write messages to the doctor or nurse, if possible.

Positive Pressure Respirators

In England and on the Continent a positive pressure type of respirator has become popular. It has the advantage of easing the nursing care of the patient, since the patient can be kept in a regular hospital bed. A tracheostomy must be performed as the machine is attached to a special tracheostomy tube which has a collar which closes off the upper passages of the respiratory tract. The machine is small and portable. Newer models permit alterations in both depth and rate of respiration. One caution is

that the rubber valve needs changing once or twice a day. A theoretical disadvantage is that with positive pressure, secretions are forced into the smallest alveoli, but this has been negated by the practical experience of those using the machine.[26] An actual disadvantage is that the machine must be detached from the tracheostomy to permit suctioning This type of respirator may become popular in the future.

Tracheostomy

Formerly it was our rule that a patient was not tracheostomized unless he had remained in the respirator for more than 24 hours and it was not possible to remove the secretions by the use of the suction machine. Now it is thought best to perform tracheostomy earlier if the indications are that the patient is not likely to leave the respirator within a few hours, particularly if secretions are difficult to handle.

Oxygen is given to the patient immediately upon being placed in the respirator. If some degree of cyanosis persists, tracheostomy is performed early. When a tracheostomy is about to be performed, the patient should be warned that he will not be able to speak temporarily but that his speech will return when the tracheostomy tube is occluded and will certainly return when he is removed from the respirator and the tracheostomy wound is permitted to close.

In performing a tracheostomy, it is important that the tube be placed below the cricoid cartilage, but not too low on the neck since this makes it difficult for the collar of the respirator to be placed in the correct position A bar is attached which pushes the upper part of the collar into the respirator, freeing the tracheostomy tube. Local anesthesia is used during tracheostomy. The anesthetist intubates the patient and breathes for him by manually squeezing on a bag filled with oxygen This permits the surgeon to operate in a field not obstructed by the moving collar. When the trachea is incised and the tracheostomy tube is ready for insertion, the anesthetist removes the laryngeal tube, permitting the insertion of the tracheostomy tube, usually a #5 or #6 silver one at the start. The patient is then returned to the respirator and the machine is turned on

The tracheostomy tube consists of an outer part, which is attached around the neck by linen tapes, and an inner part which can be removed for cleansing. Secretions are thoroughly suctioned out through the tracheostomy tube and the oxygen tube is attached to a De Vilbris atomizer Water is permitted to flow into this vaporizer through a drip so that the oxygen is moistened. This helps to prevent the formation of mucous crusts in the trachea

that the pressure valve needs changing once or twice a day. A theoretical disadvantage is that with positive pressure secretions are forced into the smaller airways, but this has not been reported in the practical experience of those using the machine. Its actual disadvantage is that the machine must be detached from the tracheostomy to permit suctioning. This type of respirator may become popular in the future.

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With the tracheostomy functioning ... piratory ... fiber ove... the patie... obstruction below the tracheostomy ... is functioning well and blow back and forth, indicating good exchange. If the fiber moves in a sluggish manner, proper respiration has not been attained. This may be due to the respirator's needing adjustment or, more likely, the tracheal-bronchial tree is partly obstructed by mucous plugs. If good suctioning through the tracheostomy tube does not clear the passages, a bronchoscopy should be performed immediately

In permitting the tracheostomy wound to close, smaller sizes of tracheostomy tubes are inserted as the patient improves until a #2 tube is in use. After this size has been reached, the tube is completely removed and the wound is taped to permit healing Another method is to cork the tracheostomy tube for increasingly longer periods until the patient can do without the tracheostomy, at which time the tube is removed

Supportive Drug Therapy

When a patient is placed in a respirator, he tends to develop ... because he cannot cough up the mu... It becomes ... ately Ge... units tw... gives the best protection ... day, and penicillin, 800,000 a fever of 101° or 102° F until he is removed from the respirator and can breathe on his own At times, a cofflator has been used ... chanical coughing to clear the ...

The ... tul... tair... tube is preferable for the patient who remains in ... balance must be main- the respirator more than 24 hours since more nearly normal alimentation can be maintained, including the use of fats, carbohydrates, proteins, vitamins and minerals Specific anticholinesterase medication can also be given through the nasogastric tube

Anticholinesterase Medication

Randt[7] was the first to recommend precipitous withdrawal of anticholinesterase medication for the patient showing obvious signs of drug intoxication who does not respond to reduction in dosage He placed these patients in the respirator after an elective tracheostomy He stated that the rationale for this type of therapy was fourfold

1 Anticholinesterase medication has been demonstrated to be ineffective in maintaining vital respiratory functions

2 The drug may be contributing to further neuromuscular junction bl(
3 The parasympatheticommimetic property of Prostigmin enhances pharyn;
and tracheal bronchial secretions, which in turn promote the developmeni
atalectasis and pneumonia
4. Minimal response may produce respiratory movements and breathing
of phase with the respirator, which defeats its purpose and leads to furt
exhaustion

Randt reports on the use of this treatment in a series of seven patie:
in crisis. Six of these patients had a remission after from three to twel
days of artificial respiration. Three of them required no Prostigmin
three to thirteen days after coming out of the respirator. Of the sev
patients, four were able to carry on relatively normal activity after bei:
discharged from the hospital. There were three deaths, one on the seven
day while in the respirator with evidence of consolidation at the right lu
base, and two others died after several months of intermittent respirat
care.

Churchill-Davidson and Richardson[14] have carried Randt's ideas
step forward. They treated a patient in myasthenic crisis with d-tub
curarine This patient had a cyclic response to anticholinesterase therap
There would be a period of improvement in muscle power after the a(
ministration of Prostigmin, followed by a gradual deterioration when tl
drug was continued After the patient was placed in a respirator (positiv
pressure type), Prostigmin was withdrawn They assumed that Prostigmi
on continued use was gradually and repeatedly poisoning the patien
Their hypothesis was that there is an alteration of response at the motc
end-plate to acetylcholine or one of its breakdown products.[27,28] Thi
altered response might be explained by an alteration in the ratio of acetyl
choline molecules to choline, the former producing depolarization durin;
their fleeting life span; and choline persevering indefinitely, producing
nondepolarizing block like that of d-tubocurarine. Therefore, they rea
soned, a myasthenic muscle which ceases to respond to Prostigmin, may
do so after a rest from treatment They gave d-tubocurarine in order tc
place all neuromuscular junctions at complete rest and treated thei
patient with injections of d-tubocurarine for a period of eight days On
the ninth day, the patient was removed from the respirator and found to
be in a complete remission which lasted for the next eleven days This
experiment and explanation is ingenious, but hardly to be recommended
for therapy at this time. The patient was brittle and swung from one type
of crisis to the other. In view of the results obtainable with aldoximes,
which are four hundred times less toxic than curare, *it is best to await*
their availability Van Spijk[29] subsequently reported three cases that he
had treated with d-tubocurarine, only one of which showed improvement

He had treated them for a period of 24 hours and found the patients were curare-sensitive, in contrast to the experience of Churchill-Davidson and Richardson

Both Schwab [30] and Grob [31] have stated that the complete withdrawal of specific therapy is fraught with hazards and makes nursing care more difficult. If some medication is given, the patient can be withdrawn from the respirator for short periods, permitting the nurse to attend to the patient

In five of our respirator cases medication was withdrawn and complete or almost complete remission occurred after removal of the patient from the respirator The patients had been in the respirator from two and one-half to seven days These remissions were of short duration and eventually the patients required the use of anticholinesterase medication in reduced amounts

Currently, when a patient is placed in the respirator, all anticholinesterase medication is discontinued for the first 24 hours If the patient is cholinergic, the overdosage effects of the drug wear off If the patient is myasthenic, it allows him to live during this period without medication and possibly lowers resistance to therapeutic agents when they are reinstituted

When drug therapy is to be resumed, the patient may not be able to talk because of a tracheostomy tube nor write because of limb weakness In such instances, as a criterion for the effectiveness of treatment, respirations may be observed by opening the vents of the respirator If the patient cannot breathe on his own for a minute or two, a Tensilon test should be performed, using 1 ml (1 mg) If marked improvement in respiration occurs with the test, anticholinesterase medication is given It is *unnecessary* to perform frequent Tensilon tests. If the patient can breathe on his own for periods up to five minutes and if he can move about in the respirator, he should not be treated with specific medication He should be permitted to breathe on his own each hour for as long as he can maintain adequate respiration As these periods become longer, he is weaned from the respirator If the patient does not breathe well on his own except after Tensilon, and especially if the patient cannot move his limbs without Tensilon, anticholinesterase drug therapy should be reinstituted after 24 hours in the respirator

Since Mytelase has the least effect on bronchial secretion, it is the drug of choice for the respirator patient The syrup of Mytelase which contains 15 mg in each 5 ml is given in a 1 ml dose Dosage is then built up to the point of maximum effectiveness as determined by the Tensilon test. It is necessary for the nasogastric tube to be in place for the use of this

form of therapy. The next most preferable drug is Mestinon which can be used as a syrup, crushed tablet, or can be given parenterally. Prostigmin is the drug of least choice because of its marked effect on bronchial secretion

Both Grob[31] and Schwab[30] have maintained life for myasthenia patients in the respirator for long periods of time, up to six months Certainly patients requiring the respirator more than a short period need anticholinesterase medication. For the prolonged respirator case a rocking bed can be substituted which can well take care of the weakened respiratory exchange We have had little experience with the chest cuirass and therefore are in no position to recommend its use except for transporting patients.

An analysis of the cases of crises at The Mount Sinai Hospital shows that of 57 patients in crises, 30 survived, but one died subsequently in secondary crisis The survival rate is 53 per cent. Patients living fall into the following evaluation:

A Remission (after cholinergic crisis)—1 patient.
B. Clinical improvement, with reduction in medication—12 patients.
C Clinical improvement, but no reduction in medication—4 patients.
D No improvement, but reduction in medication—9 patients
E. No change—2 patients
F. Worse, either with or without increase in medication—2 patients.

Of the 47 patients in myasthenic crises, 18 died, an incidence of 38 per cent Almost all myasthenic crises occurred in patients in the acute fulminating or late severe groups, which is reflected in the increased death rate of these types of myasthenic patients. Of the 20 patients in cholinergic crises, 6 died, an incidence of 30 per cent. Three patients died in mixed crises One-half of these cases had been tracheostomized. I strongly believe that early tracheostomy will prevent death in crises.

TABLE 10 *Crises*

Occurrence of Crisis After Onset of Disease	*Number of Cases in Crisis*
Up to 1 year	18
2	15
3	3
4	3
5	2
6-10	8
11-15	2
16-20	5
21-25	1

TABLE 11. Crises

Years of Survival After Crisis	Number of Patients
0-1	11
1	7
2	5
3	1
4	1
5	1
6-10	4

PREVENTION OF CRISES

Rigid dosage schedules do not give adequate control in myasthenia gravis, it is important to teach the patient to vary his dosage according to need The patient must feel free to telephone the doctor when any problem of dosage arises He must be able to recognize cholinergic side-reactions and should have atropine to combat cholinergic reaction if it occurs As pointed out previously, no severe myasthenic patient should ever take regular doses of atropine or belladonna to anticipate or prevent the muscarinic side-effects without full knowledge of the dangers of this procedure, since these side-effects are valuable signs of the approach of cholinergic symptoms

Oral antibiotics should be prescribed for use at the first sign of infection since myasthenic crisis is often precipitated by infection, particularly in patients who have a history of frequent infection This type of patient may require a daily maintenance dose of antibiotics, such as is prescribed for the rheumatic heart case.

ILLUSTRATIVE CASE HISTORIES

Case 1 A 40 year old, white, married female had an onset of symptomatology in July, 1946, with generalized bulbar and skeletal involvement. She was diagnosed in 1948 by a parenteral Prostigmin test. At the same time a thymoma was discovered by x-ray A thymectomy was performed in 1948 and there was a mild reduction in symptoms in the course of the next eight months Subsequently, exacerbation of her symptoms necessitated hospitalization for a period of one year. By 1950 this patient was at home, but required the services of her entire family and a housekeeper In the course of the next few years she had many ups and downs and was one of our pedigreed patients whom we hospitalized several times to study the effectiveness of new drug therapy In the spring of 1955, on routine x-ray examination, a recurrence of the thymoma was

found in the right chest. This was attached to the parietal pleura. The patient was hospitalized for excision of this metastatic mass. In preparation for surgery, using the conversion table given in the Chapter on Management, she was placed on 4 mg. injectable Mestinon bromide every four hours. Whether fear of undergoing surgery increased her need for anticholinesterase medication or the parenteral medication was not effective for the full four hours, the patient suddenly developed an attack of dyspnea and respiratory paralysis She was immediately placed in a respirator and suction was used to clear the secretions A short time later, the patient was resting comfortably in the respirator but she could not move her limbs A Tensilon test was performed The patient's condition improved markedly, with increased ability to breathe and to move the extremities By intravenous titration, Mestinon bromide, 6 mg, was injected, with complete relief of all her myasthenic symptoms. The patient was permitted to remain in the respirator with the machine open and was removed to her bed some five hours later after oral dosage of Mestinon bromide proved effective. A decision was made to cancel the operation at this time The mass was then treated with radiotherapy, with subsequent diminution in size. Six months later the mass (a recurrent thymoma) was removed. A right pleurectomy was also performed as there were five small thymomas present in the pleura. Currently, the patient is in comparatively good health and is able to accomplish her required daily chores

Case 2. A 57 year old, white, married female had an onset of symptomatology in 1953 which affected the pharyngeal area in the form of dysarthria, dysphagia, difficulty in chewing, nasal regurgitation of food, and dyspnea She also had myasthenic facies, but no ptosis or diplopia. She was diagnosed relatively early. A thymoma was excised through a sternal splitting operation There was no subsequent remission of any of her symptoms and the patient was slowly going downhill as a result of inanition A nasogastric tube was passed and the patient was fed by gavage She was maintained on Prostigmin Both Mestinon and Mytelase were tried, but neither was as effective as Prostigmin. When one of the newer drugs for experimental study became available, it was offered to her as a possible means of improving her symptomatology. The patient was transferred to BC-40 The dosage was 19 mg approximately every eight hours during the next 48 hours After the first 24 hours the patient felt stronger, but there was no real relief of her bulbar symptoms. During the second 24 hours there appeared to be some difficulty with her absorption from the gastrointestinal tract and the next morning the patient was having some respiratory difficulty A Tensilon test was equivocal Since there was some slight improvement after the Tensilon test, the

interne gave the patient parenteral BC-40 and parenteral Mesti
Within the hour the patient was having labored breathing with diapho
sis and gastrointestinal cramps One mg atropine sulfate was given hypodermic. Despite this injection, respiration ceased suddenly and t
patient became markedly cyanotic She was immediately placed in th
respirator and oxygen was administered, but the cyanosis persisted An emergency bronchoscopy was then performed and thick inspissated mucus was suctioned from the bronchial tree At this point the cyanosis began to recede The patient was left in the respirator, but no further atropine was ordered for fear that it would further thicken the secretions The anesthetist was called to intubate the patient and establish artificial breathing, while the otolaryngologist performed a tracheostomy The patient was returned to the respirator and was maintained for sixty hours without anticholinesterase medication A Tensilon test was then performed which markedly improved respiration so the patient was started on her previous oral dose of Prostigmin bromide Gradually she was weaned from the respirator and was able to maintain adequate respiratory exchange for periods of five to six hours Eventually she was able to remain out of the respirator during the waking hours and was returned to it at night for sleeping Eight days after crisis the patient had a sudden episode of chest pain associated with cardiac standstill and respiratory arrest All emergency measures were reinvoked Although respiration could be maintained, the cardiac standstill continued. A cut-down over the heart was made and cardiac massage instituted. Despite return of the heart beat, more than five minutes of cerebral anoxia had occurred and the patient remained comatose After four hours the patient died Autopsy revealed a massive pulmonary embolization.

Case 3 A 14 year white female had an onset of symptoms in April, 1956, with ptosis, dysarthria and limb weakness One week later, the patient developed a severe upper respiratory infection with some nausea and vomiting She vomited one of her doses of medication, but her parents did not give her another dose of medication that night The next morning the patient had severe difficulty in breathing The local physician by telephone directed the parents to give her parenteral Prostigmin The patient felt better and was brought to the office later in the morning, at which time she still appeared myasthenic and had difficulty handling her secretions, which were removed by suction She was admitted to the hospital Increased and more frequent dosage of anticholinesterase drugs was given, but the patient became more myasthenic and dyspneic Side-reactions were becoming troublesome so the patient was placed in a respirator that evening Oxygen was administered The previously prescribed antibiotics were increased The patient was kept in the respirator

for 72 hours and was kept free of secretion by frequent suction. Because she could move about freely in the respirator, no anticholinesterase medication was administered. On the third day in the respirator her menses started and her condition became worse. Cyanosis became more evident despite constant administration of oxygen A tracheostomy was performed Subsequently, the cyanosis decreased and the patient was able to move about a bit more freely in the respirator. The next morning a nasogastric tube was passed and intravenous administration of fluids was discontinued. The following morning a Tensilon test showed marked myasthenic response. Mytelase syrup, 10 mg per dose, was started. An attempt was made to wean the patient from the respirator but she resisted. Some 30 hours later, the patient requested removal from the respirator and never returned to it. After coming out of the respirator, the dose of Mytelase was reduced to 5 mg The patient was given 2000 r of x-ray to the thymic region By the time of her discharge from the hospital, she only needed 2.5 mg of medication at p.r.n. intervals, perhaps twice a day. Thymectomy was deferred in view of this improvement, which continues to the present.

Case 4 A 42 year old, white, married female had an onset of symptomatology in March, 1956, with vertical diplopia and weakness of both hands She was diagnosed in July, 1956, and treatment was begun with 30 mg. Prostigmin every two hours. Between onset and diagnosis, the patient had developed dysarthria, gagging and dysphagia. Symptoms were progressive and were only partially relieved by Prostigmin In the ensuing months she had three episodes of upper respiratory infection necessitating the use of suction and oxygen. A few days before entering the hospital in October, 1956, the patient was transferred to Mestinon bromide, 120 mg every two hours. Ptosis developed. The patient had always been emotionally labile and since the onset of myasthenia, tended to be depressed. On admission to the hospital, the patient was in obvious distress. A diagnostic work-up was unrevealing. Since the patient did not respond well to Mestinon or Prostigmin, she was transferred to Mytelase The patient was apparently doing rather well until she developed another upper respiratory infection on the seventh hospital day, with a slight rise in temperature. At this time it was noted that the patient was resistant to anticholinesterase medication She had great difficulty in breathing Despite continuous suctioning and the use of oxygen, she did not improve. The patient was placed in a respirator, and she started to run a temperature of 100° to 101° F. despite antibiotic therapy Sixteen hours later a tracheostomy was performed under local anesthesia. Following the tracheostomy, the patient was maintained in the respirator for 72 hours The patient was then permanently removed from the respirator. No anticho-

linesterase medication was given while the patient was in the respirator, and when removed, no further medication was administered for the next 72 hours The patient was transferred to Mestinon bromide when Mytelase seemed ineffective Upon discharge from the hospital, the patient's increased activity necessitated an increase in medication Subsequently, this patient had a thymectomy performed at another hospital and died postoperatively.

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CHAPTER X

Nursing Care

NURSING CARE of the ambulatory myasthenic patient is relatively simple. He is instructed by the physician as to the dosage of medication he needs. This is checked periodically by the physician and adjusted when necessary. The family of the patient is taught how to administer anticholinesterase medication intramuscularly if the necessity should arise.

Professional nursing care becomes essential if the patient enters a crisis, either myasthenic or cholinergic, develops severe infection or must undergo surgery[1] A nurse caring for a myasthenic patient must know five basic rules of nursing the proper use of equipment and machinery, the action of the drugs the patient is taking and their antidotes, the administration of proper hygiene, the anticipation of the patient's needs, and, above all, how to recognize signs of distress in time to call the physician.

In crisis the myasthenic may experience respiratory embarrassment, making it necessary for the respirator to be used The maintenance of correct pressure within the respirator is of utmost importance The nurse, by watching the pressure gauge at the top of the respirator, must see to it that the correct pressure is constantly maintained Leakage of air from any of the openings in the respirator can change the negative pressure within the machine. The opening at the head of the respirator must be properly padded so that the patient's neck is comfortable and air can neither escape nor enter The portholes which the nurse must use to administer to her patient must be bolted tightly when not in use

In the respirator the patient's personal hygiene must be carefully watched Decubitus ulcers are a very common complication Rings must be used under the elbows, heels and back The patient's position must be [illegible]

The patient who has dysarthria or who has had a tracheostomy cannot speak. If the patient can use his hands, he can write notes to the nurse on a magic slate To keep this slate always in the patient's grasp, it can be taped to the inside of the respirator or, if necessary, loosely tied with thin cloth tape to the patient's wrist

Often the myasthenic is completely helpless, not able to use his hands or speak, therefore, the nurse must anticipate many of his needs One such need is the use of the bedpan. A cardinal rule when caring for a patient

in a respirator is that he is *never* to be left alone. If the nurse must leave the room, a relief nurse *must* take her place.

The respirator can be shifted into several positions. It can be tilted upward to place the patient's head higher than his feet, or it can be put into Trendelenburg position by a jack which is at the base of the machine. The patient may also be tilted from left to right by other wheels on the machine.

Use of the suction machine is often necessary in the care of the myasthenic patient. Frequently, a tracheostomy must be performed to facilitate breathing, and a tracheostomy set must always be in the patient's room. Suctioning post-tracheostomy is of the utmost importance. The suctioning catheter is placed on one leg of a "Y" tube. No suction can be obtained until a finger is placed over the other leg. The catheter is passed into the trachea without suction, the finger applied to the open end, and suction is then maintained while the catheter is being removed. Another method is to pinch off the catheter while it is being inserted. The catheter should be washed by placing it in a basin of water and permitting suction to clear the apparatus.

Equally important is the care of the tracheostomy tube. It must be kept free of thick and hardened mucus at all times and the inner tube must be removed periodically for thorough cleaning. Vapors, both hot and cold, are often used to prevent the drying of mucus in the trachea and, if congestion is present, to loosen it. The nurse must watch for signs of cyanosis or respiratory difficulty. The doctor must be called immediately if either becomes evident.

Postoperatively the nurse must be aware that she is caring for a patient who has myasthenia gravis and has just undergone surgery. The most common operative procedure in a myasthenic patient is thymectomy. As stated previously, all emergency equipment, including oxygen, must be available. It is not always necessary to use the respirator postoperatively, but if one has to be used and oxygen must be administered, a catheter connected to the oxygen tank is placed in the tracheostomy if one is present. At times the oxygen is attached to a De Vilbris glass atomizer. Water is permitted to flow into the vaporizer through an intravenous drip regulator so that the oxygen is humidified. The level of the water in the vaporizer must be watched carefully to make certain that it does not overflow into the trachea or completely evaporate. If a tracheostomy has not been performed, oxygen may be administered by means of a face mask or nasal catheter.

Intravenous therapy is used both in and out of the respirator. The nurse should check the point of the needle periodically to see that infiltration of the solution has not occurred. If intravenous therapy has been running

for a long period of time, the needle site should also be checked for possible phlebitis The nurse must also watch to see that the solution is running properly, neither too fast nor too slowly The charting of intake and output should be done accurately, especially if the patient has had a urethral catheter inserted Care of the patient's skin must again be stressed if there are any indwelling catheters The area must be kept dry at all times, properly padded and well-powdered with a bland powder

Attention must be paid to the daily bowel elimination If the patient cannot defecate, the physician should be notified A cathartic will then be ordered *Never* is a myasthenic patient in a respirator given an enema

Feeding tubes are often used since the patient may be unable to chew or swallow [2] The following are essential rules for feeding patients through a nasogastric tube (1) The food solution is given slowly to avoid overdistention of a muscularly weak stomach (2) If the stomach seems full, feeding is omitted or stopped (3) When medication is given through the feeding tube, water is run through the tube following medication to insure complete dosage (4) If a patient is in a respirator he is kept in a level position during and for 15 minutes immediately following the feeding Otherwise the patient may regurgitate and then aspirate the material

Good mouth care must be given and the lips kept from cracking by using applicators of glycerine and lemon to swab the lips The care of the patient's eyes is also essential Crusts may form due to ptosis or lacrimation so the eyes should be gently cleansed with a mild, warm boric acid solution At times when the patient is in a respirator, there is a tendency to proptosis When this occurs, pure castor oil should be instilled into the eyes and the eyes taped closed to prevent formation of corneal ulcers

Knowledge of anticholinesterase medications is of great importance to the nurse She must be keenly aware of their specific usage, comparable dosages and, most important of all, the difference between overdosage and underdosage At all times the nurse must *double check* the type of drug and the amount of dosage she is to administer She must be sure to remember that the belladonna group of drugs, preferably atropine sulfate, is a partial antidote to anticholinesterase drugs and must always be available

The care of the hospitalized myasthenic patient requires a skilled and efficient team The nurse, who is an important part of that team, should *perform her duties in a confident, cheerful and efficient manner She will* thereby win the respect and admiration of all those around her, and especially of her patient.

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CHAPTER XI

Endocrinology

MANY INVESTIGATORS have been interested in finding a more basic physiologic error in myasthenia gravis than that which exists at the neuromuscular junction.[1] Attention has been focused on the endocrine system since this illness displays several clinical features strongly suggestive of an endocrine or metabolic disorder[2,3] These are: (1) the influence of puberty, menstruation, pregnancy and menopause in the female patient, (2) the tendency to spontaneous remissions and exacerbations, (3) the profound modifications in the clinical course sometimes occurring as a result of supervening thyroid, adrenal or pituitary disease. The pathologic changes seen in the thymus of the myasthenia patient, as described in the Chapter on Pathology are also found to some degree in numerous endocrinopathies.

These observations have stimulated the consideration of the function of the endocrine glands in myasthenia gravis both on a clinical basis and from the standpoint of experimental physiology. Pathologic reports of endocrine gland changes in this disease have thus far been few in number and in the main disappointing. At the present time there is still no convincing evidence that myasthenia gravis is a specific type of endocrinopathy

THYMUS GLAND

Normal Function

The physiologic functions of the thymus gland are unknown[14] It increases in size up to the age of puberty and then regresses. Involution of the cortex begins as early as at two to four years of age and of the medulla at puberty. In the cortex the lymphoid cells are involved early and the compressed reticular cells are replaced by adipose tissue The last elements to be replaced are the Hassall's bodies in the medulla Involution can be hastened or delayed by several factors The adrenocorticotropin or adrenal corticoids produce a marked reduction in the size and weight of the thymus gland in the intact rat The sex hormones, particularly estrogen, also cause atrophy of the thymus. This may account for the physiologic reduction which occurs at puberty. Involution is delayed by castration Growth hormone has a direct stimulating effect on the thymus

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even in the hypophysectomized animal For further details, see the Chapter on Pathology.

No evidence of the presence of any thymic hormone has been found The thymus can be removed by surgery without any observable effect in the experimental animal It may be that the breakdown products of the thymus resulting from adrenocortical secretion play some physiologic role In adrenal insufficiency and in hyperthyroidism the thymus is frequently enlarged It has also been reported enlarged in acromegaly and hypogonadism.

Relationship of the Thymus to Myasthenia Gravis

No problem has been less clarified in myasthenia gravis than that of the thymus gland and its relationship to the disorder. The presence of thymic abnormalities in myasthenia gravis[7,8] and the close relationship of tumors of the thymus and this clinical syndrome indicate that the thymus is linked with the pathogenesis of myasthenia gravis in some as yet unknown manner The simplest and most logical hypothesis is that the thymus, functioning perhaps through some endocrine-like mechanism, is the basic cause of the abnormalities at the neuromuscular junction One such theory is that the thymus gland may contain and release a blocking or depressant substance in myasthenia gravis. This work has been pursued by Wilson[9] and Schwartz[10 11] who did find such a depressant substance. Wilson states that no definite conclusions can be drawn from the results of his experiments since they are only in a preliminary phase The extracts need further purification. It must be determined whether one or more active substances are present in the extracts used The effects are not specific to extracts of thymus gland, but have been observed in extracts of lymph nodes and of voluntary muscle.

Depression of neuromuscular function was most readily obtained with extracts of the myasthenic thymus gland and that of the fetal whale thymus Calf thymic extracts have been more variable in effect, which might be due to qualitative or quantitative differences. The action of thymus extract is transient on the nerve muscle preparation or in the unanesthetized animal The effect is not reversed by Prostigmin, and Wilson assumes that although the thymic extract does not produce all the characteristic features of myasthenia gravis, this is not inconsistent with the theory that the thymus gland may release or be intimately concerned with the release of a substance which affects neuromuscular transmission.

Zack[12] suggests the possibility that the potassium present in the extracts might account for the depression observed Rider[13] failed to show any difference in the effects of thymic extracts from myasthenic and normal

subjects We are not able to relate the thymus directly to the production of a condition resembling myasthenia gravis in animals Other clinical and pathologic observations are slowly accumulating which raise serious objections to any explanation of the thymus-myasthenia gravis interrelation.

The first of these is the variable effect of removal of a thymoma upon the clinical course of myasthenia gravis [14] This effect will be discussed in Chapter XII Despite the originally highly encouraging results of Blalock [15] and others in individual cases, extirpation of a thymoma is not clearly established as beneficial. Some patients even display an increased severity of myasthenic symptoms and a rapid downhill course after operation

Secondly, many cases are reported [16] in which the evidence of a thymoma has been present for many years before any clinical signs of myasthenia gravis have developed. The most perplexing phenomenon of all is the onset of classical symptoms of myasthenia gravis in patients after a thymoma has been surgically removed Several well-documented examples are reported in the literature [17-24] and four cases have been observed in our Clinic. The interval before onset of symptoms varies from the immediate operative or postoperative state [19,20] to fifteen months after operation [21] or even as long as five years post-thymectomy [16]

In view of the peculiar aspects of the association of thymic abnormalities with myasthenia gravis, it might be best to assume until more positive data is gathered that both are caused by some as yet unknown factor or group of factors acting on different organs On the one hand, thymic changes or even neoplasia are produced, and, on the other, muscle asthenia and malfunction of a particular type result.

Pituitary-Adrenal Hormones

Recent literature [26-32] has shown that certain hormonal principles of the pituitary, adrenal and thyroid glands are capable of modifying the altered neuromuscular transmission of the myasthenic patient While the precise mechanism of the action is still not clear, further study may lead to an understanding of the underlying pathophysiology

Goñi [5] has reviewed and reported cases of myasthenia gravis in which there were associated lesions of the adrenal glands at autopsy These lesions had no specific character and were composed chiefly of an infiltration of lymphocytes, which could also be found in other organs [17,33] The early theory which compared the asthenia of Addison's with the asthenia of myasthenia has been completely changed as a result of the better understanding of the physiology and pathologic mechanisms of these two disorders Clinical adrenal gland insufficiency, such as occurs in Addison's

disease, in association with myasthenia gravis is extremely rare, according to Kane,[27] and is probably coincidental

The pituitary has been reported to be involved in myasthenia Tilney[34] published a case in which an adenoma had destroyed the posterior lobe of the pituitary body. This is the only case of this kind and it is probable that the adenoma was concomitant. No significant pituitary or gonadal abnormalities have been found pathologically in this disease.[69] A case of *myasthenia and exophthalmos has been reported in which both responded* to irradiation of the pituitary.[31] One of our cases demonstrated temporary improvement after x-ray treatment of the pituitary.

Adrenocorticotropin Hormone and Adrenocorticoids

Soffer et al [25] have shown that administration of ACTH to both animals and man causes shrinkage of lymphoid tissues, including the thymus gland Torda and Wolff [26] reasoned that if ACTH caused shrinkage of thymic tissue, it might be a valuable method of therapy in myasthenia gravis in that it would excise the thymus medically They, therefore, administered the hormone to patients with myasthenia gravis in an effort to induce remission. Early reports were most encouraging, but as more and more investigators used the therapy, it became apparent that it was an extremely hazardous procedure inasmuch as many of the patients went into crisis

The next development was the finding that if a myasthenic patient could be carried through a few days of ACTH therapy, its withdrawal would sometimes produce a rebound phenomenon which at times led to remission Subsequently, however, many negative reports appeared in the literature [28 30] Currently, the opinion is that ACTH is too dangerous to be used in the treatment of myasthenia gravis per se However, when a myasthenia gravis patient develops an inoperable thymic tumor or any secondary condition which requires the use of corticotropin, it may be used as long as the physician is aware of the hazard of inducing myasthenic crisis and the necessity for increasing considerably the dosage of anticholinesterase drug during the early phase of the use of ACTH.

At a time when ACTH was difficult to obtain, Granirer [37] suggested the use of postpartum serum given weekly to patients with myasthenia gravis. A few of his patients have done well on this regimen. These patients were later transferred to regular anticholinesterase medication without any decrease in the efficiency of these drugs

In 1939, Fraser [36] studied the 17-ketosteroids in the urine of normal subjects and patients with myasthenia gravis before and after the adminis-

tration of Prostigmin. He found no specific abnormality in the specimens from the myasthenics and no effect from Prostigmin on the excretion of the 17 ketosteroids.

Thyroid Gland

The relationship of hyperthyroidism to myasthenia gravis is of interest A prominent feature in the pathology of both diseases is the frequency of abnormalities of the thymus gland The thyroid gland was reported as abnormal in 5 of 17 cases of myasthenia gravis examined by Ringertz [33] These thyroids displayed a histologic pattern of nodular adenomatous goiter with lymphoid infiltration and occasional follicle formation compatible with a previous thyroid hyperplasia possibly associated with thyrotoxicosis Giordano and Haymond [37] also describe similar thyroid histology in their two cases, they interpret these as involutionary changes in a previous exophthalmic goiter Rowland et al [17] note the presence of toxic goiter in a patient with clinical evidence of thyrotoxicosis with myasthenia gravis and four more nontoxic nodular goiters in a postmortem series of 26 myasthenics

The differential diagnosis of these conditions is an important consideration in defining the true condition of the patient There are three possibilities (1) the patient may have hyperthyroidism alone with asthenia and muscle dysfunction, such as the acute thyrotoxic myopathy which occasionally progresses to a form of bulbar paralysis, chronic thyrotoxic myopathy or exophthalmic ophthalmoplegia, (2) he may have myasthenia gravis alone, (3) the two conditions may be present in the same patient When both conditions are present, one may precede the other or they may be almost simultaneous in onset The coexistence of myasthenia gravis and hyperthyroidism in the same patient is not common but reports of this have appeared in the literature [4, 17, 27, 32, 35, 47] Shafer and Allen [48] collected 85 cases

Most of the reported instances of the clinical association of myasthenia gravis and hyperthyroidism were made before modern methods for the delineation of the two diseases were available In 1908, Rennie [34] recorded an example of this association and further reports were made by Cohen and King,[39] Bartels and Kingsley,[40] Levy, Meadows and Gunner,[41] Schwab and Chapman,[42] Thorner,[43] McEachern and Parnell [4] Cohen and King commented on the similarities between the two diseases, pointing out that hypertrophy of lymphoid tissue, lymphocytosis, occasional glycosuria and lymphorrhages in muscle tissue are found in both conditions Dudgeon and Urquart [49] found lymphorrhages in striated muscles in eight of nine

cases of exophthalmic goiter. Thorner[43] and McEachern and Parnell[4] were impressed by the observations that there seemed to be an inverse relationship between the two diseases. They saw aggravation of the myasthenic symptoms as the hyperthyroidism was controlled and remission of the myasthenia when the Graves' disease was uncontrolled Maclean[12] confirms these observations and states that because of this "see-saw" relationship, one must not be overvigorous in the treatment of the thyrotoxicosis He uses propylthouracil instead of surgery Others are not convinced that this "see-saw" relationship is frequent.

Millikan and Haines[46] reported 25 cases of the association of these two conditions One of these responded to $1/180$ of the normal dose of curare required for curarization, while patients with uncomplicated Graves' disease respond normally to curare and to the anticholinesterase drugs[47] In their series the following time relation between the two disorders was noted

TABLE 12

	Cases	*Per cent*
Graves' disease first	9	36%
Myasthenia gravis first	8	32%
Simultaneous	2	8%
Simultaneous (?)	3	12%
Graves' first but more than five years apart	3	12%

Millikan and Haines suggest that about five per cent of all patients with myasthenia gravis have Graves' disease at some time in their illness but that only a "fraction of one per cent" of patients with hyperthyroidism have myasthenia gravis They saw no instances of the "see-saw" previously mentioned An index of the severity of the problem when both of these disorders occur in the same patient is the fact that 10 of the 25 patients in this series died

A selected number of patients from the Myasthenia Gravis Clinic of The Mount Sinai Hospital, in each of whom an unequivocal diagnosis of myasthenia gravis had been established, were studied for thyroid function by the following techniques[47]. (1) The 24-hour thyroidal uptake of I_{131} after a tracer dose (normally less than 55 per cent). (2) The plasma levels 50-51 of protein-bound I_{131} at 72 hours after the tracer dose (PBI_{131}) (normally less than 0 26 per cent of the administered dose per liter). (3) The plasma or (serum) protein-bound iodine level (PBI)[52] (normally 3 5 to 7 5 micrograms per 100 ml)

The results of these studies are presented in Table 13.

TABLE 13 *Euthyroid Subjects* *

Case Number	I_{131} *Uptake*	PBI_{131}	*PBI*
1	33	0 07	
2	19	—	4 6
3	27	—	
4	36	0 10	
5	60	0 16	4 4
6	32	0 08	
7	39	0 05	
8	50	0 09	
9	35	0 10	
10	48	0 09	
11	60	0 09	3 6
12	32	0 09	
13	37	0 03	
14	50	0 18	
15	42	0 10	4 8
16	43	0 36	
17	55	0 20	
18	22	0 08	
19	39	0 18	
20	27	—	
21	38	0 05	
22	48	0 20	
23	42	0 09	
24	40	0 05	
25	28	0 15	4 4
26	28	0 05	
27	28	0 03	
28	27	0 10	
29	19	—	
30	28	0 04	5 3
31	33	0 07	
32	40	—	
33	34	0 05	4 8
34	28	0 10	
35	42	0 08	
36	45	0 07	
37	62	0 09	5 3
38	28	—	
39	20	0 01	
40	35	—	
41	60	0 15	7 1
42	27	—	
43	29	—	6 1
44	36	0 16	
45	60	0 19	5 9

* Reprinted, by permission, from Silver, S., and Osserman, K. E. J. Mt. Sinai Hosp. 24 1214, 1957

the right costal margin. The edge was firm, sharp and nontender. The deep tendon reflexes were hypoactive and there was mild weakness on repetitive muscle movements.

Urinalysis revealed a two plus albumin on one occasion with negative albumin on repeated tests The blood count showed leukopenia with relative lymphocytosis on many occasions Blood chemistries were all normal, but the total cholesterol was 153 mg. per cent Her basal metabolic rate was plus 3 per cent, but the radiophysics laboratory reported a total plasma level of .32 per cent with a PBI of .26 per cent and an uptake of 78 per cent These findings were considered to be consistent with the diagnosis of hyperthyroidism Chest films revealed no apparent enlargement of the thymus gland

The patient was transferred to Mestinon bromide, two tablets every four hours, with marked improvement. It was noted that the patient had leukopenia, and since it was thought that this might be due to the Mestinon bromide, the patient was returned to Prostigmin therapy, with a subsequent exacerbation of her symptoms. On Prostigmin the leukopenia persisted and it was felt that the low white count might have been induced by the previous propylthiouracil therapy. Mestinon was reinstituted The patient was treated with four millicuries of radioactive iodine and discharged from the hospital after a three-week stay. Both the hyperthyroidism and the myasthenia were well controlled She was subsequently followed in both the Thyroid Clinic and the Myasthenia Gravis Clinic She was taking two tablets of Mestinon every two hours There was some residual weakness in the arms, hands and legs, and some weakness of the ocular muscles in both eyes Her dose was raised to three tablets of Mestinon bromide every three hours, on which dose it was noted that the patient was doing fairly well As to her thyroid status, at the various clinic visits it was noted that she was still nervous, still perspiring, that her hands were warm and moist and showed a slight tremor The gland remained diffusely enlarged, there was no bruit Two months later, it was noted that the estimated weight of the thyroid was 40 Gm and it was diffusely enlarged The hands were still warm and moist with moderate tremor Despite the administration of four millicuries of I_{131} the gland was still hyperactive The patient developed an upper respiratory infection and was taken to another hospital where they did not know of her past history She received no anticholinesterase medication and died from respiratory failure

Case 2 A white female, twenty-two years of age In 1946, at the age of fourteen the onset of hyperthyroidism occurred with reactions of nervousness, tremor, easy fatigability, heat intolerance, excessive diaphoresis and a thirty-pound weight loss over a six-month period Basal metabolism

rate at that time was +78 per cent She was treated with iodine and propylthiouracil and showed complete remission of all toxic symptoms Treatment was discontinued early in 1948, and in late 1949 there was an exacerbation of all symptoms Thyroidectomy was attempted, but because ... in her blood pressure and pulse rate early in the ... any thyroid tissue was ... was treated with two doses of radioactive ... h a significant improvement in her symptoms, with the exception of exophthalmos which had been a prominent feature ever since onset She married and became pregnant A therapeutic hysterotomy was performed at four months In 1953, the patient again became pregnant and began losing weight In December, 1953, the patient first noted difficulty with her voice, which became hoarse and developed a nasal quality Within days she was experiencing gradually increasing difficulty in swallowing liquids, which were often regurgitated through the nose The next symptom to develop was progressive muscle weakness, apparent as the inability to hold her head erect and difficulty in chewing Her symptoms were minimal to mild on arising and became aggravated with exertion as the day progressed Metrorrhagia developed and she was admitted to another hospital ... following an incomplete abortion She was ... of myasthenia ... ral Prostigmin bromide, 8 tablets ... n to a parenteral injection of 2.5 mg Prostigmin each morning ... ch evening before supper Atropine sulfate was given routinely with each dose of Prostigmin In April of 1954 she was referred to our Clinic where a Tensilon test revealed a cholinergic response and she was subsequently admitted to the hospital for regulation of medication

On admission, during the course of physical examination the patient became progressively dysarthric. The skin was warm, moist, delicate and smooth The hair was silky fine, and examination of the eyes revealed bilateral exopthalmus, lid lag, diminished blinking, intact extraocular ... and normal pupillary functions There was an ... no bruit was noted ... ble but there was a short apical systolic ... within normal limits ... tive movement of all muscle groups Neurolog... wise unrevealing

Laboratory procedures revealed a normal hemoglobin, urine, blood sedimentation rate and chemistries including a cholesterol of 155 mg

per cent. Chest film and electrocardiogram were normal Basal metabolism rate was plus 14 per cent and radioactive iodine uptake was 80 per cent in twenty-four hours. PBI was 9 8 gamma per cent. Her hyperthyroidism was treated with 2 millicuries of I_{131} in addition to Lugol's solution. Her myasthenia was treated with Mestinon bromide and was adequately controlled on 3 to 4 tablets every 3 to 4 hours The patient was discharged to the out-patient Thyroid and Myasthenia Gravis Clinics and did remarkably well until the tenth of May, 1954, at which time she noted increasing weakness and difficulty in speech. The patient, at home, kept increasing her anticholinesterase medication during the next four days, at which point she was readmitted to the hospital in almost complete respiratory failure and was immediately placed in a respirator Atropine was administered Physical examination showed extreme exophthalmos and complete ophthalmoplegia She could not swallow or talk and there was pooling of secretions in the pharynx. Her course in the hospital seemed to fluctuate, at times she spoke softly and at times appeared comatose. Tracheostomy was performed because of sudden onset of cyanosis within twenty-four hours of admission. She was kept in the respirator without any anticholinesterase medication for a period of thirty hours, after which time a Tensilon test revealed a myasthenic response From this point on the patient was treated with Mestinon bromide. On the third day of this admission, because of the extreme exophthalmos with severe chemosis, the patient was started on ACTH, 40 units intravenously daily, with Mestinon increased as necessary to cover the effects of the ACTH There was some improvement the next day and within three days of treatment the exophthalmos was markedly diminished and extraocular movements were almost normal As expected, the myasthenia gravis symptoms exacerbated and it was suggesed that the ACTH be stopped. She gradually showed increasing strength so that by the seventeenth hospital day she could stick out her tongue, move her jaw repeatedly and had good hand grasp Within the next twenty-four hours she began to have bleeding from various mucous membranes and was found to have a prolonged prothrombin time. She was treated with vitamin K and blood transfusion and seemed to be improving, but she died suddenly on her twentieth hospital day Postmortem examination revealed tracheobronchitis with extensive atalectasis of all the lobes of the lung, hemorrhage in the gastrointestinal tract and lungs, acute splenic softening, fibrosis of the thyroid and bilateral exophthalmos

Case 3. A thirty-five year old white female was in perfect health until February, 1954, when she developed diplopia, dysarthria, persistent salivation and generalized weakness. She was hospitalized with a probable diagnosis of brain tumor because of the high protein content in her spinal

fluid On admission, both the clinical examination and the Tensilon test confirmed the diagnosis of myasthenia gravis Routine diagnostic work-up, including radiography of the chest, was unrevealing It was noted that the patient had some exophthalmos and a I_{131} study was performed which showed her uptake to be 60 per cent Total plasma level in 72 hours was 35 and protein-bound plasma was .35, which was reported as consistent with the diagnosis of hyperthyroidism She was treated with 2.7 millicuries of I_{131} A positive Wasserman report explained the increased protein content in her spinal fluid The patient was treated for myasthenia gravis with Mestinon bromide, with good results.

The patient was readmitted to the hospital in June of 1954 because of the development of dysphagia and the subsequent onset of myasthenic crisis, which was handled without a respirator Nine milliliters (18 mg.) of Mestinon bromide was given intravenously Her thyroid status at this time was euthyroid, with an uptake of 28 per cent in twenty-four hours. Her total plasma level was 9 and protein-bound plasma was 68 Difficulties at this time were largely of an emotional nature because of the break-up of her marriage Mytelase gave good relief of dysphagia, but severe side-reactions occurred After one month of hospitalization the patient was discharged on four tablets of Mestinon bromide every four hours

In September of 1954, she developed an upper respiratory infection, with increased requirements for medication Her respirations became labored and the patient became very apprehensive She was readmitted to the hospital and was found to be in a marked cholinergic state Because of increasing respiratory difficulty she was placed in a respirator and a tracheostomy was performed She remained in the respirator for one week, was gradually weaned and the tracheostomy was permitted to close She was discharged from the hospital on 2½ tablets of Mestinon every 3 hours An I_{131} uptake was performed during this admission and was found to be 40 per cent

The patient was readmitted to the hospital in April of 1956 after she developed another upper respiratory infection She showed progressive weakness, marked salivation and an inability to cough Again the Tensilon test showed the patient to be cholinergic and for the second time she was placed in a respirator and anticholinesterase medication was stopped. After several hours, titration with Mestinon showed that one milliliter gave considerable improvement, enabling her to remain out of the respirator for 45 minutes Because of difficulty in controlling cyanosis and inability to wean the patient completely from the respirator, a tracheostomy was again performed, with marked improvement in the patient. During the next few days in the respirator, attempts were made to control her

anticholinesterase medication, which was now needed in increasing amounts until she finally reached a peak of 5 ml every three hours On the seventh of April the patient's pulse suddenly ceased after she had been out of the respirator for less than a minute. An autopsy revealed a persistent thymus and persistent purulent tracheobronchitis with atelectasis.

Gonadal Hormones

Clinically, two observations in the young female myasthenic focused attention on the possible role of the sex hormones in this condition: (1) Keynes [54] reported that symptoms of myasthenia became worse in 31 out of 65 patients in relation to menstruation. In 16 of these 31 patients, following thymectomy, menstruation had no effect on symptomatology We have found a comparable percentage (34%) of exacerbation of symptoms in the menstruating female This relationship has been noted by many investigators [65] (2) Investigators [50 69] have reported that pregnancy has an effect on the myasthenic patient (see Chapter XVI).

Estrogen, progesterone and testosterone have a multiplicity of physiologic actions. They all have a protein-sparing action, some influence on the electrolyte balance, and an interrelationship with one another and the pituitary gonadatropins that is of a suppressive nature Two other actions are of interest in myasthenia: their influence on the thymus gland and their relation to acetylcholine-acetylcholinesterase enzyme.

Venning [70] has pointed out that there is an acute involution of the thymus as well as other lymphoid organs during pregnancy. Brouha and Collin [71] have shown that this maximal thymic atrophy is found within two months after the onset of pregnancy. Selye [72] found that most hormonally active steroids influence the thymus in varying degrees, with the estrogens and the adrenocortical hormones appearing to be the most active in this respect. Ingle [73] has shown that hormones increase the muscle work capacity of rats

Numerous reports in the literature on obstetrics discuss the effect of estrogenic hormones on the amount of acetylcholine present in the uterus, placenta, serum and the red cell It has been shown that acetylcholine is formed in the syncitial villus of the placenta and that acetylcholinesterase early in pregnancy is present in high concentration in the placenta; thus, the acetylcholine exists in a reserve form [74 76] Reynolds and Foster have shown that estrogen increases the amount of acetylcholine in the uterus [77] They have shown that stilbesterol has almost no effect. Free estrogen raises the acetylcholine level immediately, while the conjugated estrogen raises the level slowly. Acetylcholine has been studied in the menstruating female in relation to the menstrual cycle, and the effects of

the various hormones on acetylcholine levels have been reported Many papers, however, deal with the pseudocholinesterase which is present in plasma and are therefore open to the criticism of not reflecting the true state of esterase activity.[78,83]

Barnes and Epperson[78] state that they could find no menstrual variation and no difference in the sexes in plasma cholinesterase levels, and they found that pregnancy lowered only the pseudocholinesterase enzyme On the other hand, Reynolds[79] shows a definite increase in acetylcholine on the second to the seventh and the twenty-second to the twenty-fourth day of the menstrual cycle

As early as 1940, Viets and Schwab[84] tried seven different endocrine preparations as therapeutic drugs in patients with myasthenia gravis, but none was found to be effective in altering the degree of severity of the condition They do not state the nature of the hormone, the frequency or amount administered to their patients On the basis of their study of the influence of pregnancy on myasthenia,[58] they made a second attempt at endocrine therapy at a later date, again with negative results They gave injections of follicle-stimulating hormones and follicle-luteinizing hormones with testosterone to the point of producing complete cessation of menses and a male pattern of hair growth without any effect on the myasthenic symptoms In 1954, they[84] treated twelve patients with testosterone without observing any benefit on the myasthenic symptoms Another negative report states that two myasthenic patients were treated with large doses of estrogenic hormones for one week without beneficial effects These authors suggest, however, that this mode of therapy be given further trial[85]

We have been treating both male and female patients with sex hormones for the past two years The hormones seem to have a beneficial effect but we await the completion of the experiment before advocating this therapy

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CHAPTER XII

Surgical Treatment

IN THIS CHAPTER, surgical treatment in myasthenia gravis will be discussed and the indications for operation presented Two major procedures have been advanced, one of which, thymectomy, has been in use for almost twenty years and has been tried in a sufficient number of patients to permit assessment of its value. The other operation, carotid sinus denervation, although also in use for a number of years, has not been performed upon any great number of patients and has only been tried in European and South American clinics, thus, this operation will be discussed only as an experimental procedure at this time. Since radiotherapy is intimately associated with thymectomy, its use will be partially covered in this chapter as well as in a separate chapter.

THYMECTOMY

The thymus, enigma of histologist, physiologist and pathologist alike, has provided the clinician with problems which are still far from solution.[1] In the Chapters on Pathology and Endocrinology the relationship of the thymus to myasthenia gravis has been stated.

Historical Development

The first operation on the thymus gland in which apparent success in the treatment of myasthenia gravis followed removal of a thymic tumor was performed by Blalock in 1939[2] However, even at the present time there is no unanimity of opinion concerning the value of thymectomy. This lack of unanimity after nineteen years of performing the operation has led Westerberg,[3] Mackay,[4] and Schlesinger[5] to state that thymectomy is evidently not of great value or it would not have been so difficult to determine whether or not it is a helpful procedure.

At first, all patients regardless of age, sex or the presence of a thymoma were operated upon for relief of myasthenic symptoms At The Johns Hopkins Hospital, after performing a number of thymectomies, they discontinued the operation because of disappointing results. Keynes[6] in England early pointed out that in those patients with a tumor of the thymus gland the results were definitely worse than those attained in patients who did not have such a mass He began to separate his statistics on the basis of the presence or absence of thymoma.

Eaton et al.[7,8] published statistics and changed their opinion on the advisability of the operation from pro to con to pro at various times. Schwab and Leland[9,10] published a statistical survey of those patients who had had the best results from thymectomy and reported a sex difference. They found the following in their study of 78 cases treated with thymectomy and compared to a control group.

1. Myasthenic symptoms were not improved in patients with thymoma
2. They could find no evidence of benefit in males Thymectomy is contraindicated for males, especially if the onset of myasthenia occurred after thirty years of age.
3. In females without thymoma, 53 patients or 63 per cent benefited from this operation as compared to 34 per cent in the control group The mortality, including operative deaths, was 15 per cent in the thymectomized female compared to 28 per cent in the control group

They concluded that the indication for thymectomy should be the young female under thirty years of age who has had the disease for less than five years and does not have a thymoma.

Keynes[6] divided his cases according to results following this operation "A" and "B" were those patients who were quite well or greatly improved following thymectomy and "C" and "D" those cases with little or no improvement In his 1945 and 1949 series he found that 60 to 70 per cent of his patients fell into the "A" and "B" classes. He criticized Eaton, Clagett and Grob for not breaking down their figures by listing the thymoma cases separately Keynes does not make a distinction between the male and female patient, a distinction which Simpson has reconfirmed.[11] He quotes Ross[12] who found that remissions in the course of medical [illegible]

Sixty-seven of 100 patients, excluding those with thymic tumors, were markedly benefited by the operation The age of onset of the myasthenia did not appear to be a significant factor in results, while the briefness of the duration of the syndrome before surgery did seem to be an influence in obtaining good results An interesting sidelight of Keynes' report is that he accepts as remission residual symptoms of some muscular weakness which he feels is irreversible. One or more ocular muscles may not respond to drug therapy. He states that drug therapy can be stopped without affecting the patient's health in these cases Here again, he quotes the work of Russell[13] which shows that there possibly are irreversible changes in myasthenia gravis which neither thymectomy nor drug treatment can reverse

Brea et al.[14] report the results of 24 thymectomies in patients ranging

from 13 to 60 years, 20 of them being female Three patients had thymoma. Two patients died Eighteen showed excellent or good remissions, seven of which were complete remissions. These patients were examined by Goñi and Lanari

In an attempt to evaluate indications for thymectomy, Eaton and Clagett reviewed all the cases operated on at the Mayo Clinic, using the statistical analysis advocated by Schwab and Leland They reported that their data were remarkably similar to that of Schwab and Leland in that there were good results with female patients, while, statistically, good results in the male patient could not be demonstrated. Fifty-four per cent of female patients from whom a non-neoplastic thymus was removed obtained complete remission or considerable improvement, whereas only twenty per cent of control female patients obtained comparable status without surgery. Only 13 per cent of female patients treated surgically became worse or died, whereas 34 per cent of the control female patients were in those categories Results with older women were not significantly different from those in younger females.[15]

Viets[16] in adding the reports from America to those of Dunlop[17] found that although Keynes and Ross found 67 per cent to be in Keynes' "A" and "B" classification, the combined reports of other centers showed only 40 per cent Dunlop suggests that this difference occurs because Keynes has been more radical and has performed surgery in a larger proportion of milder cases He also states that the early and sustained improvement shown by some patients makes it difficult to escape the conclusion that thymectomy has been instrumental in causing the alteration in the patient's clinical state.

Arguments Against Thymectomy

Investigators who do not see any particular value in thymectomy base their opinion on the following factors

1. From the experimental work in animals so far accomplished the thymus cannot be related directly to the production of a condition resembling myasthenia gravis As stated in the Chapter on Endocrinology, extracts of the thymus gland do have a depressant action, but this action does not resemble that of ordinary blocking drugs nor is it influenced by Prostigmin[18,19] Well-documented cases have been reported in which thymoma existed prior to the onset of myasthenia but myasthenia developed only subsequent to the removal of the tumor. This type of situation casts doubt upon the theory that the thymus gland secretes a substance which causes the myasthenic syndrome and makes it conceivable that both the thymic tumor and the myasthenia result from the same cause[19]

2. If the thymic gland has some influence in myasthenia gravis, why isn't the patient who has a thymoma, and thus a marked increase in thymic tissue,

TABLE 15 *Thymectomy (No Tumor)*

		Mass. Gen. 1953–367 pts.				Johns Hopkins 1953–202 pts.				Mayo Clinic 1955–374 pts				Keynes 1945, 1949, 1953			Mt. Sinai 1958–325 pts.	
	Eval. Key	*Surgery*		*Medical*		Surgery		Medical		Surgery		Medical		Surgery			Medical	
Sex		F	M	F	M	F	M	F	M	F	M	F	M	1945	1949	1953	F	M
No. of Patients		53	25	51	23	25	19	77	41	30	17	34	23	33	120	200	212	113
Remission	A	21%	8%	13%	16%	12%	22%	14%	17%	17%	17%	5%	13%				15%	
Considerable Improvement	B	42%	16%	21%	40%	38%	16%	22%	12%	37%	17%	15%	18%	60%	65.8%	70%	30%	
Moderate Improvement	C	7%	20%	28%	16%					20%	17%	15%	18%				17%	
Same	D E					21%	21%	22%	12%	13%	30%	31%	35%	24%	25.8%		12%	
Worse	F	15%	21%	13%	8%	—	—	12%	15%	3%	6%	26%	8%				8%	
Death	G	15%	32%	25%	20%	29%	42%	30%	41%	10%	12%	8%	6%	15%	8.3%		16%	
A plus B Results		63%	24%	34%	56%	46%	35%	30%	29%	54%	34%	20%	31%	60%	65.8%	70%	45%	

from 13 to 60 years, 20 of them being female. Three patients had thymoma Two patients died Eighteen showed excellent or good remissions, seven of which were complete remissions. These patients were examined by Goñi and Lanari

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	Eval Key	Mass Gen 1953–367 pts Surgery		Mass Gen Medical		Johns Hopkins 1953–202 pts Surgery		Johns Hopkins Medical		Mayo Clinic 1955–374 pts. Surgery		Mayo Clinic Medical		Keynes 1945, 1949, 1953 Surgery			Mt Sinai 1958–325 pts Medical
Sex		F	M	F	M	F	M	F	M	F	M	F	M	1945	1949	1953	F M
No of Patients		53	25	53	25	25	19	77	41	30	17	51	23	33	120	200	212 113
Remission	A	21%	8%	13%	16%	12%	22%	14%	17%	17%	17%	5%	13%	60%	65 8%	70%	15%
Considerable Improvement	B	42%	16%	21%	40%	36%	16%	22%	12%	37%	17%	15%	18%				30%
Moderate Improvement	C	7%	20%	28%	16%					20%	17%	15%	18%				17%
Same	D E					24%	21%	22%	12%	13%	30%	31%	35%	24%	25 8%		12%
Worse	F	15%	24%	13%	8%	—	—	12%	15%	3%	6%	26%	8%	15%	8 3%		8%
Death	G	15%	32%	28%	20%	28%	42%	30%	44%	10%	12%	8%	8%				18%
A plus B Results		63%	24%	34%	56%	48%	38%	36%	29%	54%	34%	20%	31%	60%	65 8%	70%	45%

helped by this operation, rather than, as is the case, the patient with a normal-appearing thymus?

3. Objection has been raised because the results reported do not seem to be logical Why should the female and not the male be helped by this operative procedure?

4. Another objection is that the stress of surgery acts like the stress of ACTH and the rebound phenomenon seen with stress might possibly account for any good results.

5. Since the myasthenic patient is seeking a cure and major surgery is represented as a possible means of inducing remission, the hope aroused in the patient may give such a psychological lift that this may be the cause of improvement rather than the operation itself.

6. The results of medical management are not inferior to those of surgical treatment.

Opposed to the performance of thymectomy as a routine measure are Grob,[20] Jørgensen,[21] Hoefer,[22] Bergh,[23] Johnston,[24] Bonduelle,[25] and Ferguson [26] Some of these men do recommend thymectomies in selected cases It should be noted that some series are small and that conclusions drawn from them may not have the same validity as those of authorities who have had larger series to evaluate. Hoefer [22] reports that they have had spontaneous remissions in 33 of 95 medically treated patients and that a few of these patients have had several spontaneous remissions.

Grob,[20] in a study of 202 patients with myasthenia gravis followed at The Johns Hopkins Hospital from one to thirty-four years, found 13 per cent were in complete or near complete remission, 25 per cent had improved moderately, 20 per cent were unchanged and 10 per cent had become worse. One-fourth had had complete or near-complete remission at some time, the average length of the remissions being 4 6 years Forty-four patients who were thymectomized and 40 who had radiation to the thymus had only a slightly better course than 118 patients who had undergone neither Fifteen patients had thymoma; ten of these had a rapid, fulminating course with death ensuing whether or not thymectomy was performed.

Jørgensen [21] treated 12 cases with thymectomy. Two died immediately after operation, one died five years later. A follow-up of the nine remaining cases revealed that eight reported improvement and one patient with a malignant thymoma was better for one year and then experienced an exacerbation. Seven could reduce their dose of Prostigmin and two had had to increase the daily dose. He concludes that thymectomy is justified if the patient's life cannot be rendered tolerable by administration of Prostigmin He has no control series.

Bergh [23] reported 12 cases, two with thymoma and four postoperative deaths He concluded that myasthenia gravis should be treated conserva-

tively until convincing evidence in favor of the operation is presented. A study of the age and sex of his patients shows that most of them were females in the 21 to 50 year age group.

Recently, Ferguson[26] reported on the medical management of myasthenia gravis. He quotes Kennedy and Moersch[27] who reviewed 87 cases followed for an average of four years prior to the availability of Prostigmin and at a time when thymectomy was not practiced. They noted complete, spontaneous remissions in 27 patients. These remissions ranged in duration from one month to 15 years, the average being 2.2 years. Ferguson studied 85 cases of myasthenia gravis from 1932 to 1954 which had been treated optimally with Prostigmin or Mestinon. Seventy-five of these cases were treated medically. The 60 survivors were reexamined in 1954.

Thirty-two of Ferguson's patients had remissions, some repeatedly, so that there were a total of 81 remissions in the entire series. The average duration of remission was 4.9 years. He concludes that a decision to advise thymectomy may be made if the condition is generalized at an early stage and cannot be controlled adequately with Prostigmin. The extension of the ocular form to the generalized type might also be an indication for operative treatment.

Garland and Clark[28] have studied 60 patients, reporting on them in 1956. The mortality rate was between 9 and 16 per cent. Twenty-four patients had complete remissions lasting from days to seven years. Six patients were subjected to thymectomy. He states that there was no evidence that thymectomy had helped any of these patients. None of the six had a thymic tumor. He does not give the age or sex of these patients.

The reports just summarized demonstrate that medical management of myasthenia gravis yields results which apparently are not too inferior to those reported from centers performing frequent thymectomy. Unfortunately, the semantics of the word "improvement" is cause for some hesitation in comparing the results of medical and surgical therapy. "Remission" is a clear word which leaves no room for misunderstanding when the reports of one group are compared to those of another, whereas the definition of "marked improvement" is not exact. It is dependent upon the clinical appraisal of the investigator who is classifying the results of therapy. If all cases of medical and surgical treatment could be appraised with the same evaluation key, a clearer picture of thymectomy might be established.

The necessity of excluding patients with ocular involvement only is important (Group I),[29,35] since these patients do remarkably well no matter what treatment is used. Grob,[29] in 1953, drew attention to the need for segregation of the ocular group for purposes of assessment. This was done by Eaton et al[8] in 1953, but Keynes'[6] figures do not seem to take this

factor into account as the functional studies by Ross do not refer to it.

The fact that thymectomy has been performed by all investigators reveals the need for other than medical management in selected cases which do not respond to drug therapy.

Rebuttal

1. Wilson[18,19] studied the thymus glands removed surgically by Keynes from patients with myasthenia gravis. He examined 42 of these glands and prepared an acetone and later a water extract from them. These extracts showed evidence of a neuromuscular blocking action when applied to biologic preparations such as the sciatic gastrocnemius and phrenic diaphragm. The effect of d-tubocurarine was used as a control standard. Extracts taken from normal adult thymus showed no such blocking action. In the myasthenic thymus he found three particular groups which he labeled "X," "Y" and "Z." The highest activity of neuromuscular block was in the "X" group but this was not due to a greater weight or size of the gland. He found his "X" group were removed from patients who attained "A" and "B" clinical results in Keynes'[6] postoperative classification (complete or almost complete remission). His "Y" and "Z" groups corresponded to the "C" and "D" clinical responses in Keynes' series where there was little or no significant effect from thymectomy. The question of the onset of myasthenia after a thymectomy for thymoma cannot be answered at this time. A possible explanation might be that the entire thymus gland was not excised at surgery.

2. Objection number two can be answered by the fact that patients with thymoma are definitely more ill and their prognosis is worse than other patients whether treated surgically or medically. Percentage-wise, thymomas appear mostly in Group III, which has the poorest prognosis. The natural history of cases with thymoma precludes a true evaluation of thymectomy. Furthermore, if the thymoma is removed without excising the remaining thymus tissue, it can be postulated that the patient may go into thymic storm postoperatively due to hypersecretion from the remaining tissue.

3. Although the reason for the significance of sex and age in relation to thymectomy is not apparent at the present time, these factors are statistically important, as has been shown by the findings of investigators such as Schwab,[9] and Eaton and Clagett[7] who state that by performing this operation on patients selected according to indications of sex and age, the remission rate can be increased by about 100 per cent. Keynes[6] and Simpson[11] do not feel that sex is important. Viets[20] has begun to advocate more surgery for male patients.

4 Many patients have had major operative procedures other than thymectomy without comparable remission

5. Undoubtedly, a psychological lift from surgery can be anticipated but that this is the sole cause of improvement can be refuted by such experimental procedures as that which shows that following thymectomy the patient loses his hypersensitivity to curare [37] On the other hand, three myasthenic mothers have been reported who were thymectomized and later gave birth to children who had transient neonatal myasthenia gravis [38 40]

6 Investigators in favor of thymectomy make the following statements. (a) The mortality from the surgical procedure is, at most, four per cent and recently has been reduced almost to zero in centers where frequent thymectomy is performed. (b) The mortality rate of thymectomized patients, including postoperative mortality, is lower than the mortality rate in medically treated patients These surgical remissions remain more constant and last longer than in the medically treated patient. Even if the patients do not achieve an "A" or "B" result, their myasthenia is more stable and more amenable to drug therapy.

The Author's Viewpoint

After reviewing the above arguments, sound reasons can be found for and against thymectomy. A review of the medically treated cases at The Mount Sinai Hospital shows that 77 patients (24 per cent) have had a total of 84 remissions; that 43 patients are still in remission, that the aver- [illegible]

occur in the first two years of illness. Remissions may not be as long-lasting as those reported after thymectomy Forty-five per cent of the medically treated cases were definitely improved ("A" and "B") This compares fairly well with results reported by various investigators [9] following thymectomy When improvement is estimated by clinical classification, it can be seen that Group III and IV show the poorest results (Table 16)

TABLE 16

Clinical Classification		Improvement (A, B, C) (Per cent)
Group I	–Localized	81%
Group II	–Generalized	67%
Group III	–Acute Fulminating	21%
Group IV	–Late Severe	25%
Group V	–Muscle Atrophy	45%

The over-all death rate is 18 per cent, of which 15 per cent is attributable to myasthenia per se. These figures are similar to the mortality figures in the thymectomized series. When the death rate is tabulated by clinical classification (Table 17), it can be seen that patients with the acute fulminating type (Group III) or the late spread (Group IV) have a much higher percentage than the other groups.

TABLE 17. *Death Rate*

Types	*Number of Patients*	*Percentage*
Neonatal	0	0%
Juvenile	3	10 6%
Group I	2*	0%
Group II	12	10 0%
Group III	20	61 0%
Group IV	*14*	*44 0%*
Group V	6	30 0%

* Nonmyasthenic deaths.

Seventeen patients have been thymectomized, too small a series for evaluation. Pathologic examination of these thymus glands showed that two were benign thymomas, seven were malignant thymomas and eight were normal Seven of the eight normal thymuses were removed from *females under the age of 30 with a duration of their myasthenia* of less than five years. No "A" (complete) remissions occurred in this group The distribution of thymectomy by clinical classification shows that none were performed in Group I, four in Group II, seven in Group III, four in Group IV and two in Group V (table 18).

TABLE 18

Clinical Classification	*Cases Thymectomized (Per cent)*
Group I	0%
Group II	3 7%
Group III	27 0%
Group IV	14 0%
Group V	12 0%

In deciding on thymectomy in the patient without a thymoma, the indications of Schwab and Leland and Eaton and Clagett are followed, i e., the premenopausal female who has had myasthenia for less than five

years Since results of medical therapy are excellent in Juvenile and Group I cases, thymectomy is indicated only for the patient who is not well controlled with drug therapy (Groups III and IV, with selected cases from Groups II and V)

The reports from centers that perform frequent thymectomy, that remissions last longer in the thymectomized patient than in the medically treated, must be given weight and perhaps are an indication for performing thymectomy in more Group II patients The fact that we limited our selection of patients for thymectomy to certain clinical classifications may account for the absence of "A" remissions in our thymectomized cases The patients operated upon are living, whereas similar cases in these clinical classifications which were not operated upon died within one to two years of the onset of their myasthenia Another argument in favor of thymectomy in selected cases is the statement of surgically orientated therapists that even if the patient is not improved clinically post-thymectomy, he is more stable and easier to control with drug therapy than the nonthymectomized patient

Schwab,[41] one of the most staunch advocates of thymectomy, nevertheless seems to favor some selection of cases in his statement that a 20 year old female who has a mild case of the disease of a year's duration and who only takes two to three tablets of medication a day and feels perfectly well should not necessarily submit to surgery. He states that they have done thymectomies on very few such mild cases, and he agrees that the severity of the disease as well as its duration and its response to medication has to be very carefully considered before undertaking a procedure which is both an economic burden and time-consuming and still carries a surgical risk of death. Schwab considers thymectomy to be an elective procedure which should not be used to alleviate crisis Although Johnston[24] reports a case successfully brought out of crisis by thymectomy, this is not an accepted procedure

Surgical Method

The best procedure in thymectomy is a sternal splitting operation The sternal may be split longitudinally or horizontally The longitudinal operation gives the surgeon direct view of the anterior mediastinum, can be performed rapidly, and does not open the pleural cavities The horizontal procedure is through a transthoracic approach, which is important to the female in that it avoids a midline scar. There is less painful healing and wide inspection of the entire thoracic area is possible. This incision requires the opening of both pleural cavities and tends to make the postoperative course more stormy. In any event, if a pleura is opened the

patient is treated with suction under water drainage postoperatively. The opening of the pleura may be necessary in cases of malignant thymoma in which the tumor has invaded the pleura The pericardium when invaded by thymoma may be opened and the part involved excised with the tumor. When thymoma is present, the entire thymus as well as the tumor should be excised. Complete hemostasis must be attained before the chest is closed It is not advisable to drain the anterior mediastinum for if the patient later requires respirator care, the drain may act as an avenue for infection to reach the anterior mediastinum.

Preoperative preparation, anesthesia and postoperative care of the patient are described in the Chapter on the Care of the Surgical Patient. Recently, Schwab[41] has been pre-treating patients with a normal thymus with x-ray and has found a five per cent increase in remission rate in cases so managed Results of thymectomy do not necessarily become apparent immediately postoperatively, although some patients may have an immediate reduction in drug requirement and a few have a need for increased dosage. The real results of thymectomy appear during the first year after operation Viets[36] has recently stated that favorable results may be as late as two to three years in appearance, but it is hard to attribute, in so variable a disease, good results to thymectomy at such a late date. It is important to tell the patient in whom thymectomy is to be performed that final evaluation must be delayed at least one year.

Thymoma

The problem of thymectomy in the myasthenic patient who does not have a thymoma has been discussed What is the indication for thymectomy in the patient who does have a thymoma? Most investigators feel that since 25 per cent are potentially malignant, these tumors should be removed regardless of the fact that the patient has myasthenia gravis. In nonmyasthenic patients with thymoma, total thymectomy rather than excision of the tumor alone is the procedure of choice inasmuch as 17 cases have been reported in which myasthenia gravis has subsequently developed From reports of the operative procedures it is not known whether total thymectomies had been performed in these cases.

Thirty-six patients (11 per cent) at The Mount Sinai Hospital have had thymoma No instance appeared in the neonatal or juvenile groups It is important that thorough x-ray visualization of the anterior mediastinum be performed, otherwise small tumors may be overlooked It should also be re-emphasized that the presence of calcium in such a tumor as visualized by radiographic methods does not preclude malignancy.

TABLE 19 *Thymoma.*

Clinical Classification	*Male*	*Female*	*Per cent of Classification*
Group I	2	2	5%
Group II	2	8	8%
Group III	7	6	40%
Group IV	1	5	19%
Group V	1	2	15%

An analysis of table 19 shows that in Groups I and II thymoma is relatively rare, that there is a four to one preponderance of females in the generalized form, paralleling the four to one female to male distribution in this group In the acute fulminating Group III, 7 of 9 males display thymomas, whereas only six (25%) of these females have thymoma

We must recognize that the patient with thymoma is much more ill, has a higher operative mortality rate than the patient without thymoma and is more likely to have a stormy postoperative course A few single cases and some small series have been reported in which patients who did have a thymoma in conjunction with myasthenia gravis were helped by the operation [42, 43]

Williams [44] has reported 13 cases, 9 of which were operated on after having received 4,000 r to the anterior mediastinum preoperatively Of the nine patients treated with both radiotherapy and thymectomy, one died of metastasis and four responded well. Viets has stated that administration of radiotherapy before operation for thymoma should be given a more extensive trial in other clinics Williams treated four cases by x-ray alone Only one responded well In three cases treatment had to be interrupted because of the development of radiation mediastinitis

Keynes [45] reports that 41 of his 260 patients with myasthenia gravis had thymoma, an incidence of 15 4 per cent He was able to find ten other cases which he added to his series for analysis Of the 51 cases, 22 were male and 29 female. Keynes feels that the term "malignant" has been too rigidly interpreted and he gives reasons why all these tumors are in some respect malignant He states that the symptoms are always severe, the response to Prostigmin is slow and sometimes incomplete, and the onset is rapid and severe in all cases with tumor. Before 1947 he treated all of these cases with a primary operation He had 11 such cases; only three survived for more than two years and only one was alive at the time of his 1954 report.

Since 1947, he has treated these cases with x-ray radiation before performing surgery He so treated 26 patients, using 4,000 r in divided doses

over a period of four weeks or longer prior to surgery. Subsequently, 21 of these 26 cases came to surgery. One was inoperable and the patient died eighteen months later. Of the remaining 20, four died, one was no better, three were improved at first and later relapsed, eight showed considerable improvement and four were quite well and asymptomatic He makes a strong point for treating these cases with x-ray radiation first and subsequently removing the thymoma by surgery.

Carotid Sinus Denervation

In an attempt to influence the course of myasthenia gravis, denervating the carotid sinus was started in France. A number of reports have come from Thévenard,[46] and subsequent reports have come from various sections of Europe,[47] the most recent being from Mertens [48] in Germany and Yoel [49] from South America This operation was first performed in 1943 by Leger Thévenard reports twenty cases of his own. Fifteen were cases of severe myasthenia gravis with unquestioned diagnosis He states that much is unknown about the physiology of the operation but that favorable effects occurred in varying degrees in 60 per cent of the cases The operation has an antimyasthenic effect, producing stabilization of the disease. It takes time for the full effect to occur, and there may be a delay of up to a year. The rationale for this operation was based on animal experiments which showed that carotid sinus denervation is followed by adrenocortical hypertrophy The early reports on cortisone and ACTH which showed favorable results in the treatment of myasthenia gravis (which were later disproved) were the inspiration for the continuation of this work.

Stepien and Herman [50] operated upon ten patients and reported improvement in eight of them They rejected thymectomy as being too dangerous and uncertain an operation, preferring the removal of the adventitia from the carotid sinuses Mertens [48] has collected 28 cases published in the literature, including four of his own He states that results have been reported favorable in 60 per cent of the cases and that age does not play a role. There are no complications from the operation He states that his own results were not as good as those reported in the literature and he cannot personally recommend the operation In his four cases he first used Novocain block anesthesia to assess results. Case 1 was considered a good result. The second case was excellent for nine months and then exacerbation occurred His other two cases did not do well at all. Yoel and Alurralde [49] report four cases, in which they claim excellent results in all.

If a thymoma is present, the denervation operation is done first and

when the patient responds, a secondary thymectomy is performed The operation is performed under local anesthesia. Thévenard is of the opinion that a bilateral operation must be performed.

No such operation has been reported in this country Until more reports are available, this operation cannot be recommended, since results are minimal and are not different from developments seen in the ordinary course of the disease.[16]

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CHAPTER XIII

Radiotherapy to the Thymus

Radiotherapy to the anterior mediastinum has been used in myasthenia gravis in an attempt to induce remission or to improve the course of myasthenia in patients without thymoma, as well as in the treatment of thymic tumors associated with myasthenia gravis.

This form of therapy is not to be undertaken lightly. As has been pointed out,[1] irradiation may produce radiobiologic effects either on the irradiated individual himself or, through him, upon his descendants. In the elderly individual the latter objection is nullified. Somatic effects vary according to the different organs or tissues affected and range from slight and reversible disturbances, such as cutaneous erythema, to the induction of leukemia or other malignant diseases. The effect of radiation on the whole body must be considered However, in treating a patient who cannot be controlled with drug therapy, the radiobiologic effects are only of academic interest.

The normal thymus extends from the isthmus of the thyroid down to the level of the fourth costal cartilage It rests on the aortic arch, the great vessels of the heart and the pericardium Because of the nature of the chest cavity in this region, it is difficult to administer very large doses of radiotherapy to the thymus Treatment is usually given daily, shortly after a dose of anticholinesterase medication in order to obtain optimal muscular cooperation from the patient.

Jones et al[2] have pointed out the necessity of starting treatment with small dosages of only 50 to 100 roentgen units. Too large an initial dose or too rapid an increase may aggravate the myasthenic symptoms In addition to the usual reactions to mediastinal x-ray therapy, such as nausea, leukopenia and erythema, patients are prone to attacks of pyrexia with atypical pulmonary infections which may precipitate increased myasthenic symptomatology, even to the point of crisis. When such conditions occur, radiotherapy must be suspended and appropriate medical therapy instituted After the episode is over, x-ray therapy may be cautiously resumed.

Radiotherapy to the Nontumorous Thymus

Because of the lack of unanimity regarding the indications for thymectomy in myasthenia gravis, radiotherapy has been used as a form of treatment in an attempt to stop the downward course of myasthenia. Ken-

nedy[3] was one of the first to advocate this procedure in treatment He prescribed the administration of 200 roentgen units on three consecutive days for a total of 600 roentgens. He treated his patients by giving one such course yearly for a period of five to seven years and claimed that this procedure could favorably influence the course of the disorder My colleague, Dr. L I Kaplan, who was associated with Kennedy, has seen a number of these patients and has sent a few of them to our clinic In one patient who had an exacerbation of symptoms, the administration of 600 r returned her to an "A" remission within a few weeks This procedure, which had fallen into some discard, has recently been readvocated by Westerberg.[4]

In 1953, Grob[5] reported the results of administration of 2,000 roentgen units to the anterior mediastinum in a series of 40 patients He reported that 40 per cent of his patients were moderately improved, but statistically the improvement was not much greater than that seen with medical treatment alone or with thymectomy. Jones et al[2] state that radiation of the non-neoplastic thymus has been sporadically practiced for a number of years and that its value has been difficult to assess The patient's age, duration of the disease and response to anticholinesterase drug therapy determines his selection for this treatment

TABLE 20 *Evaluation of X-Ray Treatment*

Patients' Current Status	*Number of Cases without Thymoma*	*Number of Cases with Thymoma*	*Total*
A	1	1*	2
B	10	4	14
C	5	1	6
D	2	0	2
E	4	3 (1*)	7
F	6	5 (1*)	11
G	6	6 (4*)	12
Totals	34	20	54
		Male	*Female*
		16	38
Percentage of Improvement A-B-C	47%	30%	41%

* Also thymectomized

In The Mount Sinai Hospital group, 54 patients were treated with radiotherapy. Thirty-four had no demonstrable thymona and were treated with 600 to 2,000 roentgen units to the thymus Side-reactions with any of the doses were minimal. Side-reactions to radiotherapy may be treated

by daily injections and/or oral use of pyridoxine 100 mg in conjunction with the use of Dramamine or promozine. Almost one-half of the patients improved on radiation therapy and in the other half no additional deterio-

of the

patient who is not eligible for thymectomy, i.e., the male and the elderly female, or patients in Group IV with a late spread with degeneration of their clinical status despite optimal anticholinesterase drug therapy.

The optimal radiotherapy dose is not known. Evaluation regarding the importance of dosage could not be determined from this small group. Currently, we have discarded the 600 r and use the 2,000 roentgen unit dose This dose can be administered through a single portal over the sternum by the administration of 2,400 roentgen units in air in a period of two and one-half to three weeks.

This is too small a series upon which to base definitive conclusions, but it seems to point to the value of this form of therapy when drug treatment becomes ineffective.

Radiotherapy in Thymoma

If a thymic tumor is not treated radically, there is usually progression of myasthenic symptomatology to the point of ultimate fatality. Primary surgical extirpation has a high morbidity and mortality.[6]

TABLE 21 *Treatment of Thymoma*

Type of Treatment	*Total No of Patients*	*Living*	*Dead*
X-ray	13	11	2
Thymectomy	4	1	3
X-ray and thymectomy	7*	3	4
No treatment	12	4	8
	36	19	17

* Two thymectomies not performed at our hospital.

A false sense of security may be engen-
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thymus is composed of two elements: epithelial and lymphocytic. The lymphocytic elements are highly radiosensitive and since they usually compose the largest part of the tumor, the x-ray appearance may be quickly changed by radiotherapy Histologic studies of thymic tumors removed after x-ray therapy, however, show that the epithelial elements remain relatively unaffected even though the tumor has undergone considerable

shrinkage because of destruction of the lymphocytes Therefore, radiotherapy alone is usually regarded as inadequate. At The Mount Sinai Hospital, five of twenty patients treated with radiotherapy alone were improved with a dose of 4,000 to 6,000 roentgen units to the thymus, whereas fourteen became worse or died on the same dosage Three cases developed a disturbing feature. while receiving radiotherapy, the requirement for anticholinesterase medication decreased, at times sharply, but the patient's clinical response to new dosage levels was less predictable and less efficient than at previous higher dosages If attempts to increase medication were started at the lower levels, patients developed clinical cholinergic reactions, which were confirmed by Tensilon tests. Complete resistance to specific drug therapy developed and two patients died while in a respirator

Radiotherapy to the thymus alone [illegible] the amounts of 4,000 r to 6,000 r

that is available, this dose can be administered through a sternal, a right and left parasternal and a posterior mediastinal field The dose to each field depends upon the anterior-posterior diameter of the patient's chest. In the average case the dose is about 2,000 to 2,400 roentgen units (in air) per field Four to five weeks is required to administer this dose

Radiotherapy in Conjunction with Surgery The poor results shown in Table 21 on treatment of thymoma with thymectomy alone or in conjunction with x-ray may be due to the type of patients selected for surgery These patients were elderly and seriously ill myasthenics in whom operation was ordered because there seemed no hope unless a radical approach was undertaken. The four deaths occurred in the group of patients so treated early in the series In the Chapter on Pathology, it was shown that 25 per cent of thymomas are malignant in nature Because of this fact thymomas must be radically treated whether they occur in conjunction with myasthenia gravis or not As pointed out in the Chapter on Surgical Treatment, preoperative radiation of the tumor with 4,000 r in a period of four weeks prior to surgery may be prescribed Improvement is usually slow Two months after the end of x-ray therapy the patient may be thymectomized It may be necessary to wait for a longer period in order to bring the patient to optimal condition for surgery

Local Metastasis within the Chest Cavity In the Chapter on Pathology, it was pointed out that thymomas spread by local invasion within the chest cavity. When tumors recur, they exhibit the same degree of radiosensitivity as the primary growth If only a single nodule recurs, it should be treated as was the parent tumor, i e, with radiotherapy followed by excision These single nodules act similarly to metastastic nodules of thy-

roid adenomas and are very slow-growing. The advisability of surgery has been questioned on the basis that if there is one metastasis, there must be more, even if they are not demonstrable by x-ray visualization One case, at secondary thymectomy, had five nodules on the parietal pleura, only one of which was visible on x-ray. A pleurectomy was performed, with good results. If untreated, the metastases may invade the great vessels, giving rise to a superior venal caval syndrome, or they may involve the lung

The treatment of the myasthenic patient who has a thymoma is, at best, difficult. Each case must be approached individually and treated in light of the age of the patient and the severity of the myasthenic symptoms.

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CHAPTER XIV

Care of the Surgical Patient

WHEN A PATIENT with myasthenia gravis requires surgical intervention, proper preparation of the patient is of utmost importance. The primary requisite is to have a team consisting of the general practitioner, internist or neurologist who will guide the case, the surgeon, the anesthetist, and the otolaryngologist who will handle respiratory problems necessitating bronchoscopy and/or tracheostomy Naturally, if surgery is an emergency, the details of the preparation must be accomplished quickly. When the patient comes to elective surgery, the physician must take sufficient time to bring his patient to the operating table in an optimal condition Ideally, surgery should be performed during a remission, as severe cases are poor risks

Elective Surgery

The patient should be admitted to the hospital a few days prior to surgery whether it be for thymectomy, thyroidectomy, hysterectomy, or any other surgical procedure. At our hospital, the patient is admitted to the Medical Service since the resident staff and internes are always available on the floor When necessary the nutritional state of the patient must be improved, especially in those who suffer from dysphagia If need be, gavage feedings, including vitamin therapy, is resorted to [1]

By proper management techniques the patient is brought to the most ideal therapy status with anticholinesterase drugs A parenteral form of drug therapy will be required on the day of surgery and the first few postoperative days, thus, Mytelase cannot be used as it is not given parenterally. The choice lies between Mestinon and Prostigmin Since Mestinon has fewer side-reactions, it is the drug of choice If the patient has previously been tried on various drugs and Prostigmin proved to be the most effective one for the patient, he should be prepared with Prostigmin. The techniques discussed in the Chapter on Management, with particular reference to the Tensilon test, are used to determine optimal dosage Once the dosage is established, the patient is maintained for 24 to 48 hours on oral medication One or two days prior to surgery it is essential to treat the patient with parenteral anticholinesterase medication to determine the proper amount and timing of this form of treatment

Originally, the intravenous route was used, employing a 1200 ml flask of solution containing the amount of the drug required for a 12-hour pe-

riod, with the drop rate adjusted so that 100 ml. of solution was administered each hour. If 25 or 26 drops are permitted to flow per minute, the patient should be well maintained. To calculate the amount of anticholinesterase required, the conversion table on page 159 is used. For instance, if the patient required two tablets of oral medication every two hours, then he would require 1 mg. of Prostigmin every two hours or the addition of 6 mg to the 12 liter flask. He would require four times this amount of Mestinon, for a total of 24 mg.

This method is difficult since it requires constant observation of the drop rate and it is possible for patients to become mildly myasthenic and then mildly cholinergic on this regime. Schwab[2] uses the intravenous technique at the Massachusetts General Hospital. As an experiment, we performed cholinesterase level determinations at five-minute intervals on the blood of patients receiving intravenous anticholinesterase medication over a period of 175 minutes. The rate of flow was kept constant except at such times as the experimental conditions were varied. The graph of the cholinesterase levels was far from a straight line. Because of the clinical problems and the results of the above experiment, we now use the intramuscular route to administer anticholinesterase drugs.

Close attention must be paid to the time element for administration of drugs In most cases the time interval is almost the same for oral and parenteral medication, but each case must be individualized. After the proper amount and timing of drug dosage has been established, the patient is so regulated that he receives his medication one-half hour before time for anesthesia This timing of medication is then followed during surgery, if necessary It has been pointed out that ventricular fibrillation may occur when anticholinesterase drugs are administered during anesthesia[3] Only occasionally has an operation been prolonged to the point of giving a second dose. Respiratory exchange and other significant signs noted by the anesthetist must be carefully evaluated to determine the patient's need for medication

During the preoperative days the patient is taught to breathe and cough properly in order to help himself during the postoperative period Patients should not be operated upon electively unless they have a good cough. If surgery must be performed in myasthenics with weak cough reflex, elective tracheostomy should be done before the patient leaves the operating room. It has been suggested that the patient be shown the respirator and that he lie within the machine so that he becomes accustomed to it in the event that it should be needed. In special instances we use this technique in the patient who is emotionally secure, or if, on the contrary, there is an unreasonable fear of the respirator, we allow the patient to familiarize himself with it, finding this is less damaging than the

anticipation. Most patients have such a strong fear of surgery, however, that it is inadvisable to allow the respirator to be seen.

The normal preoperative routines are followed, i.e., the blood type and Rh factor are determined and blood is reserved at the bank, laboratory procedures such as urinalysis, blood counts, etc., are performed.

It is advisable during the preoperative period to use mild sedatives in small doses to help the patient's morale. We have used meprobamate (Miltown and Equanil) and encountered no undue effects although this type of drug is theoretically contraindicated since it causes muscle relaxation. With precautions, we also use promazine and its derivatives, Thorazine, Sparine, Compazine, and, of course, the old stand-bys, phenobarbital and chloral hydrate. Demerol is probably the best preoperative sedative and is prescribed in the amount of 75 mg. one hour before the operation. Myasthenics have a lowered tolerance for morphine. Atropine and scopolamine should not be used preoperatively since they tend to thicken the bronchial secretion and may mask overdosage of the anticholinesterase drugs. Preoperatively the patient is started on parenteral antibiotics, preferably Combiotic, 2 ml. twice a day. Schwab et al.[2] have pointed out the dangers of giving myasthenic patients enemas since unaccountable death has occurred following this procedure. It is best to prepare the patient with catharsis and avoid enemata. Females are operated upon post-menses to attain the best period of their cycle's variation.

All members of the operating team should meet the patient during the preoperative period so that the patient's confidence is established before surgery. Special nursing care is started with the day of operation.[5]

Emergency Surgery

In the emergency case there is not enough time to exercise the extreme care that can be followed in the elective case. A Tensilon test is performed to determine the need for anticholinesterase medication. If the patient has a markedly myasthenic response, his usual dosage can be given parenterally or, if need be, an intravenous titration may be performed, if *extreme* care is taken to avoid *overdosage*. Since preparation for the operation always takes a few hours, there is usually sufficient time to bring the patient to reasonable optimal condition before anesthesia is given.

Anesthesia

Two important rules must be observed in anesthetizing the myasthenic patient. As has been pointed out, myasthenia gravis patients are particularly sensitive to curare and *must not* receive the drug as a relaxant. It has also been demonstrated that ether and chloroform[6] have a curare-like

action and *must* be avoided With these exceptions, these patients may receive any other type of anesthesia They may have local anesthesia and spinal anesthesia since the central nervous system is not involved in myasthenia gravis. Nitrous oxide and cyclopropane with oxygen may be used for inhalant anesthesia In emergency surgery spinal anesthesia may be the best procedure because of the possibility of recent ingestion of food Patients who are extremely nervous may be given a weak solution of sodium pentothal intravenously to keep them asleep In the elective case, particularly if the chest is to be opened, as in thymectomy, inhalant anesthesia is the safest and best means

The patient is prepared by intubating the larynx. The throat is cocainized and local anesthesia of the larynx is accomplished with an injection of 1 ml of 20% cocaine through the skin just above the cricoid. Anesthesia is started in the routine manner, and when the patient is asleep, the anesthesia is continued through the intubated tube. In this manner, the anesthetist can maintain respiration for the patient by alternate contraction and relaxation of the anesthesia bag. This is particularly important if the pleura must be opened to remove adherent thymic tissue.

At the end of the operation the lungs should be thoroughly inflated and washed with oxygen During major thoracic surgery the patient may be attached to a cardiographic oscilloscope so that the heart action may be observed throughout the operation.

A number of papers have been published on the use of anesthesia in these patients[7 12] Lande[9] used local anesthesia, 10 ml of procaine, for carotid sinus denervations For thymectomy he found that general anesthesia was best. He rejected all products which irritated the respiratory tract, such as ether or trichloroethylene, and found that the best gas inhalation was nitrous oxide or cyclopropane. If he needed a relaxant, he used decamethonium or succinylcholine chloride. He used endotracheal intubation to insure proper oxygenation throughout the operation and repeated intratracheal aspiration to avoid any blocking of the respiratory tract. The patient must be protected against pulmonary atelectasis and collapse.

Bergh[8] found that myasthenia is a contraindication to the use of relaxants, especially curare Succinylcholine chloride may be given safely He reports the case of a Bantu with combined thyrotoxicosis and myasthenia gravis in which he had to resort to a relaxant and used succylmethonium chloride since the patient coughed and strained with the general anesthesia even though he was intubated. The patient withstood an initial dose of 25 mg with only slight respiratory depression not preceded by fasciculation. A further 100 mg. were given slowly, with marked

respiratory depression but not complete apnea In another report he states that succinylcholine chloride is the only relaxant to use

Dundee[11] again states that the patient is sensitive to curare and Flaxedil, which cause a neuromuscular competition block. Decamethonium acts by a depolarization block, and myasthenics show a normal response to it MacKenzie[12] states that no relaxants are needed when cyclopropane is used

Foldes[13] has an entirely different approach to this problem than other authors[14] He states that the noninvolved muscles of the myasthenic patient are less sensitive to depolarizing muscle relaxants than those of normal individuals Furthermore, the involved muscles may have an increased sensitivity to these compounds, and the block produced would be a typical, nondepolarizing, curare-type block, reversible by Prostigmin, Tensilon or similar compounds Consequently, the dose of depolarizing relaxant necessary to produce adequate surgical relaxation in the noninvolved muscle might be a severe overdose to the involved muscle Foldes suggests the careful use of d-tubocurarine or Flaxedil in these patients The initial dose of d-tubocurarine should be 0 3 mg If this does not produce relaxation, additional doses should be given three minutes apart until the desired relaxation is obtained The development of apnea should be avoided in these patients Assisted rather than controlled respiration should be employed Fractional doses of 0 3 mg or more of d-tubocurarine should be given as required The initial dose of Flaxedil should be 5 to 10 mg In our opinion, the use of d-tubocurarine or Flaxedil cannot be recommended until further corroborating experience is obtained

Preparation of a patient for anesthesia involves proper use of anticholinesterase drugs without the use of belladonna derivatives, which can produce inspissation of bronchial secretions and mask overdosage For preoperative sedation it is best to prescribe Demerol A slow intravenous perfusion of 5 per cent glucose in saline is begun in case medication or blood may have to be administered during surgery Anesthesia is started with cyclopropane The patient is intubated and carried with positive pressure anesthesia during thymectomy Very rarely, if ever, should relaxant drugs be used in these cases When the operation is completed the lungs are thoroughly inflated with oxygen Anticholinesterase medication should be given *only* as indicated throughout the operation.

During surgery, if respiratory arrest occurs when the anesthesia is other than through intubation, immediately *start* artificial respiration on the table Give 0 2 ml (*2 mg*) Tensilon intravenously If respiration is re-established, administer predetermined dose of Prostigmin or Mestinon intravenously If respiration does not resume after Tensilon, *do not* give anticholinesterase medication. Intubate patient and initiate bag-breathing

for the patient. When the operation has been completed, a tracheostomy is performed.

Postoperatively the patient is sent to a recovery room fully equipped to handle all types of respiratory emergency, with members of the team keeping constant watch over the patient. After the patient has fully reacted, he is returned to his bed.

A stand-by respirator, emergency bronchoscopy and tracheostomy sets must be immediately available. Suction sets and oxygen must be used as necessary. Routine tracheostomy is not performed at the operation.

The patient is followed closely postoperatively to determine the need for anticholinesterase medication. If a thymectomy has been performed, a sudden decrease in drug requirement may occur from a few hours after the operation to 24 to 48 hours later. If a routine order is left for anticholinesterase drugs, a cholinergic reaction may be induced. On the other hand, the shock of surgery may temporarily increase the need for anticholinesterase medication and routine therapy will not be sufficient. Postoperatively the Tensilon test as a means of management is a most helpful procedure Occasionally, intravenous titration can be useful in determining changes in the need for anticholinesterase drugs. In England, Greene[13] tracheotomizes the patient and withholds anticholinesterase drugs postoperatively. If ventilation difficulty occurs, a positive pressure respirator is connected to the tracheostomy tube (cuffed). In this manner, cholinergic reactions are avoided

Particularly in the postoperative case must all the safeguards mentioned in the Chapter on Crisis be carefully observed Enemas must not be given Antibiotics are administered routinely. The patient must be watched for the development of respiratory infection, atelectasis or pneumothorax Excessive secretions are removed by suction. Sedation is used sparingly. If these precautions are taken, one has the satisfaction of carrying the patient through a hazardous procedure with a fair amount of ease.

For the mild myasthenic patient requiring minor surgery such as dental extraction under general anesthesia, it is still wise to admit him to the hospital and have the anesthetist from the team administer the anesthesia

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CHAPTER XV

Psychotherapy

Brolley and Hollender[1] have reported on the psychological problems of patients with myasthenia gravis. They studied twelve patients, finding many defects in living common to those observed in patients with other chronic diseases but also some that seemed specific to myasthenia gravis. Since it is easier to hear unpleasant facts when someone is standing by to provide support than it is to obtain them from cold print, and since the element of hope can be stressed and anxieties can be handled in a personal interview, such an interview with the myasthenic patient is considered obligatory by these authors. Once the diagnosis is made, they recommend that the patient be told the name of his condition, that the disease is chronic, and that myasthenia is a treatable but not a curable disease at the present time. Finally, as with diabetes, the patient should be told that medication will have to be taken indefinitely.

The reaction of the patient will depend upon how he is given the above facts. The impact of the diagnosis and explanation is not always absorbed at the first visit but may be fractionated and delayed, so that the final reaction may occur even as late as one year after the diagnosis is made. Brolley and Hollender feel, naturally, that one must be very careful in ward rounds not to impart information that the patient should not have. They have found that useful information concerning the patient's adjustment to his disorder can be obtained from the attitude of the patient toward taking medication. Much of the adjustment can be understood in terms of reaction to fear and dependency To a limited degree, myasthenia gravis is a two-phased illness: a primary phase of disability and a secondary phase of rehabilitation which usually starts when medication is first given The patient's adaptation to the problems of these two phases depends upon his previous personality make-up.

The symptoms of myasthenia gravis are intensified by emotional upsets, more specifically, by anger and envy. The effect of emotion is possibly a direct one on the skeletal musculature We have become convinced of the importance of psychologic problems in our patients by observing some that have been thrown into myasthenic crisis by the hearing of bad news, and, conversely, we have seen a case in severe myasthenic crisis go into spontaneous remission merely by the husband's bringing flowers and writing poetry to her as he did when she was being courted

Meyer[2] of the Psychiatric Liaison Clinic at The Johns Hopkins Hos-

pital has been interested in myasthenia gravis and has noticed that certain patients have outbursts of emotional excitement which aggravate the myasthenia. The early reports in literature considered myasthenia gravis a neurosis In the myasthenic there are the same psychiatric syndromes, such as schizophrenia, depression, etc., as may be found in other individuals, and these have to be treated with an excessive amount of care

In a series of one hundred cases of myasthenia, eleven had histories of episodes of unconsciousness Hysteria evidently blots out the motor mechanism, resulting in flaccidity of musculature and a term of unconsciousness that resembles catalepsy. The instinct of death-feigning in animals is deep-rooted and appears in human beings Another word for this is "freezing," a reaction which results in either rigidity or flaccidity. The former may pass into the latter. This has been seen in man when under great anxiety (combat fatigue). The tone of the muscles increases, which leads to rigidity and may go on to flaccidity and finally withdrawal of the personality Great stress in myasthenia gravis is most dangerous and can arise either from the outside (situational) or from within (psychological) Meyer has not been able to undertake psychoanalysis with myasthenic patients because of the anxieties aroused by this procedure

The myasthenic patient who does poorly is mainly the dependent person with marked ambivalance about his dependency, and the super-independent person. These people, for instance, fight the respirator because basically they cannot trust other individuals to take care of them. This type uses the musculature as a defense against anxiety.

The physician is the cornerstone in the treatment of the myasthenic patient. He must be careful to give the patient comfort, confidence and honest guidance without making the patient suspect that this is just a "bedside manner." At least half an hour should be taken for a calm discussion of the implications of myasthenia gravis with the patient after the diagnosis has been established The basic physiology should be discussed in simple terms The fact that the brain, spinal cord, nerves or muscles are not permanently damaged in myasthenia gravis should be stressed It should be pointed out that the defect is a "short-circuit" at the point where the nerve impulse enters the muscle, that currently drugs are available which help to overcome this "short-circuit" It should be stated that to have any chronic disorder may be unpleasant but the myasthenic patient has a most hopeful prospect, especially since there is no pathologic defect, and that if and when the cause of the condition is discovered, he will be completely well

In the meantime, drug therapy may return him to 90 per cent of normal capacity and there is always the hope and expectation of spontaneous or induced remission At the same time, the patient should be warned

that the clinical course may first be downhill with extension of symptoms to include other muscle groups. This information must be given cautiously and always with a most hopeful attitude.

Explain to the female that she may marry and bear children. Point out that myasthenia is not an hereditary disease, as far as we know, and that if the patient does give birth to a child, at most the child may have a transient, neonatal form of myasthenia and will lose all signs of the condition in the first weeks of life.

Patients always ask how much rest is required. The answer is that they will need more rest than a normal person but that they should lead as normal a life as possible. The milder cases are permitted mild athletics, such as swimming, golfing, etc. Discuss occupation and attempt to adjust the patient to his work without changing the type of employment. Short rest periods are recommended during the day, particularly after work and during the weekend. Patients are permitted to drive an automobile with certain precautions, such as driving during the most effective period of their medication. If medication does not completely relieve diplopia, an eye patch for one eye may be suggested. Diet is adjusted to the caloric needs of the patient and no "fad" diets are permitted If the patient feels a need for vitamins, he is not discouraged, but it is pointed out that vitamins have no specific role in myasthenia gravis

The patient should be encouraged not to hide his disorder, but to lead as normal a life as is compatible with his symptomatology. Finally, the patient should be encouraged to use the telephone freely to communicate with his physician This gives him a feeling of assurance, and we have found that this privilege is rarely abused.

These people need a tremendous amount of encouragement. It is the duty of the attending physician to maintain a cheerful and hopeful attitude toward the patient's condition. The more serious psychiatric case suffering from severe depression must be seen by the psychiatrist. As pointed out in the Chapter on Associated Diseases, some of these patients may require shock therapy, which is not contraindicated because of the myasthenia. Mild sedation in the form of the newer tranquillizers or chloral hydrate may be prescribed for the less serious emotional disturbances. These and other drugs are fully discussed in the Chapter on Associated Diseases.

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CHAPTER XVI

Obstetrics

THE EFFECT OF PREGNANCY on myasthenia gravis has impressed many authors Since the available reports have involved only small numbers of cases, it has been impossible to reach any definite conclusions or reliably predict the effect of pregnancy for any particular patient. Instances have been reported of both exacerbation and remission during the course of pregnancy In 1931, Laurent[1] described a patient who had had seven pregnancies. In the first two pregnancies remission occurred, whereas in the last five, severe exacerbation took place and each pregnancy terminated in abortion Kennedy and Moersch[2] reported in 1937 on seven myasthenics in whom twelve pregnancies had occurred. In seven pregnancies the myasthenic symptoms were not affected In five pregnancies the patient's myasthenic symptoms became exacerbated, but four had a remission after the termination of the pregnancy. The authors do not mention the effects in the postpartum period

A detailed study was reported by Viets, Schwab, and Brazier[3] in 1942 They found that in most cases pregnancy "profoundly affected the course of myasthenia gravis." In their cases, usually there was a moderate relapse in the first trimester, with partial or complete remission in the second and third trimesters.

In 1945, Wilson and Barr[4] reported a case with progressive exacerbation of symptoms, and in 1948 Harris and Schneider[5] reported similar cases in which remission did or did not occur at the termination of pregnancy. Harvey,[6] in 1948, observed that pregnancy had a variable effect but that exacerbation always occurred at the termination of the pregnancy In 1953, Fraser and Turner[7] reviewed 14 cases of myasthenia gravis in which pregnancy had occurred They noted a tendency to relapse during the first trimester, but concluded that there was no indication for termination of the pregnancy They found that one-half of their patients experienced exacerbations in the early postpartum period and concluded that this constituted the greatest period of danger.

Schaposnik[8] reviewed the literature and found that pregnancy usually had some effect on myasthenia gravis, causing either exacerbation or remission, but that in a few patients there was no noticeable effect Also, an irregular course of exacerbation and remission might occur in the same pregnancy. There were different effects in various pregnancies in the same

woman. Pregnancy markedly precipitated the course of the myasthenic symptoms in some women

Schlezinger,[9] in 1955, reported on four patients in whom six pregnancies had occurred. Again, there was a mixture of reactions In his first case the pregnancy had no effect the first trimester, but an exacerbation occurred in the last two trimesters. In his second case, myasthenia developed three months after a third pregnancy, and in the fourth pregnancy a remission occurred during all trimesters which lasted until the third postpartum month In the third case, both the first and second pregnancies were initiated by exacerbation during the first trimester, followed by distinct remission which lasted until the second and eighth days postpartum respectively In the fourth case the exacerbation was striking and occurred during the last trimester, with a partial remission after birth.

In discussing the Schlezinger paper, Kosovsky, Speert and Osserman[10] reported on 33 pregnancies as seen in 22 myasthenic patients Thirty-two per cent of the patients showed a definite remission during the pregnancy, 34 per cent showed no change in the myasthenic state, and 34 per cent showed a definite relapse associated with the pregnancy All symptomatology patterns were usually established during the first trimester of the pregnancy and there was very little change during the second or third trimester, except in two cases. In those patients who had repeated pregnancies, each pregnancy had its own influence on the myasthenia gravis and did not necessarily follow the pattern of the earlier pregnancy.

There were six therapeutic abortions and seven spontaneous miscarriages in this series The occurrence of the spontaneous abortions bore no apparent relation to the degree of severity of the myasthenic symptoms which the patient presented In the six cases treated by therapeutic abortions (these were the more seriously ill patients), interruption of the pregnancy did not change the severity of the myasthenic symptoms Following spontaneous abortion, marked symptomatic improvement was observed.

Delivery and labor were normal provided adequate anticholinesterase medication was given. Prior to 1937, myasthenia gravis was considered an indication for cesarean section, but this no longer applies. The decision to section should be governed purely by obstetric considerations The character of the labor was unaffected by the predelivery status of the patient. It is important to keep the patient at optimal neuromuscular function to the extent that this can be accomplished by anticholinesterase medication.

A three-month postpartum follow-up of most of the patients usually reflected the myasthenic status exhibited during the pregnancy. In those

cases showing postpartum deterioration the physical burden on the mother of the newborn may have been an added factor

A study of The Mount Sinai Hospital series revealed that 25 patients had 36 pregnancies. Some of these cases were previously reported[10] These 36 pregnancies eventuated in 28 live infants, 6 of whom were diagnosed as having transient neonatal form of myasthenia Five patients had the onset of myasthenia either late in the third trimester or in the postpartum period

Of those patients carried to full term, 11 showed definite improvement of symptomatology during pregnancy, 9 became worse and 8 showed no noticeable change. Improvement or exacerbation usually occurred in the first trimester and generally set the pattern for the remainder of the pregnancy Two patients lost their improvement in the ninth month and two others in the postpartum period

Reviewing these results and those published in the literature,[11] one can conclude that interruption of pregnancy is not indicated because of the exacerbation of myasthenic symptoms Those cases in which the pregnancy was aborted therapeutically did not show spontaneous clinical improvement postoperatively In cases in which the myasthenic symptoms had become exacerbated, marked clinical symptomatologic improvement was observed following spontaneous abortion

The patient should be followed closely by the obstetrician and physician, the latter seeing the patient at monthly intervals to adjust dosage of anticholinesterase medication as indicated, using all the techniques discussed in the Chapter on Management When the patient enters the hospital for delivery, the physician is notified as well as the obstetrician. In the first early stages of labor, anticholinesterase medication is given orally. As the labor advances, parenteral medication is used, following the conversion factors in the table on page 159 An attempt is made to regulate the timing of the medication so that a dose is received one-half hour before the actual delivery This is done in an effort to protect the baby from neonatal myasthenia In the last five deliveries in The Mount Sinai Hospital series, three babies were born healthy infants but within the first few days showed this form of myasthenia Probably, the protection afforded by the timing of this last injection to the mother delayed the appearance of the myasthenia.

In only one case was there uterine inertia which may have been caused by the myasthenia Slow intravenous injection of Pitocin corrected this condition

The anesthesia used from the latter part of the first stage of labor through the delivery is individualized for the patient Local block with procaine is preferred Inhalants such as nitrous oxide and oxygen may be

used for the first stage and cyclopropane for the actual delivery. Barbitu ates may be used sparingly. Scopolamine, since it is related to the bella donna group, is contraindicated. If the obstetrician wishes to use Deme rol, it may be administered. An episiotomy with application of lo forceps has been the routine procedure.

Immediately after delivery the mother is observed in the delivery roon for any untoward symptoms for one or two hours. The infant, afte routine examination and therapy, is sent to the premature nursery so tha he can be closely observed by trained personnel for the early appearanc of myasthenic symptoms These symptoms usually do not occur until lat on the first or the second day of life.

Obstetric considerations are the only guide used in induction of labo or as indications for cesarean section.[12]

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CHAPTER XVII

Pediatrics

MYASTHENIA GRAVIS in infants and children is not so rare as it was once considered to be This disease in children was first recognized in 1877 by Wilkes [1] and in 1879 by Erb.[1a] Viets [2] in a historical review of myasthenia gravis to the year 1900 quotes eight cases of this disorder in children Only eight cases were recorded in the literature from 1908 to 1930 [3 10] With the introduction of the Prostigmin test, the diagnosis was made more often. Four reports appeared in the decade of the thirties [11-14] In the decade of the forties, sixteen reports are recorded in the literature [15 30] Since 1950, over fifty reports have been published dealing with myasthenia in children [31 83] In 1956, Teng and Osserman [84] reported 209 cases of myasthenia in infants and children recorded in the literature Since that report, innumerable letters have been received telling of other cases currently under treatment which have not appeared in the literature. Tether,[85] for instance, states that he has seen many children with myasthenia An analysis at The Mount Sinai Hospital of 325 cases shows that 33 were children at the time of onset of symptoms, an incidence of 10 1 per cent.

In 1942,[18] the first case of myasthenia gravis in a baby born to a myasthenic mother was reported in detail Subsequently, the term "neonatal myasthenia gravis" was used to describe the transient type and "congenital myasthenia gravis" was used for the persistent form in a child whose mother was not myasthenic.[25] The latter group was further subdivided into "congenital" and "acquired" types depending on age of onset [63] We use the term "juvenile myasthenia gravis" to clarify "congenital." Symptoms may develop at birth or at any time during the growing years.

NEONATAL MYASTHENIA GRAVIS

Although the number of reported cases of neonatal myasthenia gravis has not been large, reports have recently been appearing more frequently In the first reported case [18] of neonatal myasthenia, the infant died of respiratory failure on the seventh day despite treatment with Prostigmin. In 1944,[22] the birth of myasthenic infants in two successive pregnancies of a myasthenic woman was reported. Other cases have been described which are summarized in Table 22 [18,22,26 28,30,37-40,44-46,51,52,63 66,79]

TABLE 22 *Transient Neonatal Myasthenia Gravis* *

Author	*Sex*	*Onset*	*Therapy*	*Duration*	*Results and Remarks*
Viets & Brown, 1939	?				3 cases, no detail, 2 of these quoted by Kibrick
Strickroot et al, 1942	F	3rd day	Prostigmin bromide, 2.5 to 5 mg each feeding		Sudden death on 7th day, respiratory failure (?)
Wilson & Stoner, 1944	F	Birth	None		Died on 4th day
	M	Birth	None		Improved several weeks, then complete recovery.
Ford, 1949	?	2nd day	Neostigmine, no details	7 days	Complete recovery.
Labranche & Jefferson, 1949	M	2nd day	Started on 7th day, Prostigmin bromide, 2 mg q4h for 3 days, increased to 4 mg.		Treatment maintained 4 months
Stone & Rider, 1949	F	No detail	Started on 3rd day, Prostigmin 0 07 mg i m; neostigmine bromide 2 mg q3h for 1 day, then 1 mg q3h	13 days	Complete recovery.
Nilsby, 1949	M	Birth	Prostigmin methylsulfate, 0 1 to 0 15 mg t i d. to q i d	21 days	Complete recovery
McKeever, 1951	M	22 hours	Neostigmine bromide 1 mg. each feeding, 2 5 mg, for one dose From 8th day 1 mg. every other feeding	14 days	Complete recovery.
Holt & Hanson, 1951	F	1st day	Neostigmine bromide, 2-1 mg q3h for 16 days	17 days	Complete recovery.
Geddes & Kidd, 1951	F	2nd hour	Prostigmin methylsulfate 0 05 to 0 125 mg q4h, ephedrine 1 66 mg per rectum	36 days	Complete recovery.

* Reprinted, by permission, from Teng, P., and Osserman, K. E J. Mt Sinai Hosp. 23.711, 1956.

Author	Sex	Onset	Therapy	Duration	Results and Remarks
La Riche & Rosevar L., 1951	F	Birth	Prostigmin methylsulfate 1/10 mg i m q4h for 10 days, *then 1/8 q4h*	2 months	Complete recovery
Gans & Forsdic, 1953	M	Few hrs after birth	Started 5th day neostigmine methylsulfate 0 05 mg i m, followed by 3 mg bromide with each feeding, increased to 3 75 mg, atropine 1/600 q4h	11 days	Complete recovery
Fraser & Turner, 1953	M	2nd day	Neostigmine bromide q6h	12 days	Complete recovery
	?	No detail	None	21 to 28 days?	Complete recovery
Bryan, 1954	M	1st day	Prostigmin methylsulfate 0 25 mg i m, then 1 mg t i d	7 days	Complete recovery
Kibrick, 1954	F	Birth	Neostigmine bromide 3 mg *each feeding, then 1 5 mg* q3h	20 days	Complete *recovery*
	M	Birth	None	9 days	Complete recovery
	F	Birth	None		Died on 3rd day
	F	Birth	Neostigmine, no details	3 months?	Treatment maintained for 3 months, complete recovery.
Moore, 1955	F	Birth	Neostigmine 0 125 to 0 5 mg q4h Changed to Mestinon bromide 1 to 1 75 mg q4h on 10th day Daily test with Tensilon	6 weeks	Complete recovery
Geddes, 1955	F	1st day	Prostigmin methylsulfate 0 05 to 0 15 mg q4-6h	7 days	Complete recovery
Schotland, 1955	F	Birth	Prostigmin methylsulfate 4th day 0 05 mg test dose 2 mg Prostigmin bromide q4h	7 weeks	Complete recovery
Rowland,	F	Birth	Prostigmin methylsulfate 0 5 mg as test. 0 2 mg q4h	7 days	Complete recovery.

Author	*Sex*	*Onset*	*Therapy*	*Duration*	*Results and Remarks*
Tether, 1955	M	35 hours	Neostigmine, dose not given	10 days	Complete recovery
Teng & Osserman, 1956	M	1st day	Prostigmin bromide, 1 mg t i d	5 days	Complete recovery
	M	Birth	Mestinon bromide 0 25 mg (H) p r n.	14 days	Complete recovery

A study of these cases showed that there was no correlation between the severity of the infant's symptoms and the duration of the mother's illness or the severity of the mother's myasthenia during pregnancy. The literature reveals three cases[26,28,49] in which thymectomy performed on mothers prior to pregnancy did not prevent signs of myasthenia gravis from occurring in their three infants at birth.

Incidence

Babies with transient neonatal myasthenia gravis are born of mothers affected by the same disease. However, the majority of infants born to myasthenic mothers are not so affected. In 1951,[37] 36 deliveries of myasthenic women were observed in which only three babies had transient myasthenia of the neonatal form In 1953,[46] 14 pregnant myasthenic women were observed Six of these 14 delivered, with one set of twins, a total of seven babies Six infants were normal and one was myasthenic. In our series, six of 28 live births had a transient neonatal form of myasthenia.

Clinical Picture

An analysis of the 27 cases reported in Table 22, plus four recently observed, shows that the onset of symptoms occurred at birth in 16 cases, the first day of life in 7, the second day after birth in 6, the third day in one. No details were available for one.

The symptoms and signs of myasthenia gravis in children are different than those noted in adult patients, and in newborn infants the clinical course and symptomatology, especially of the eyes, further differs from that observed in children.

Symmetric muscular weakness is a feature in infants affected by this disorder These infants are described as being limp, motionless or having feeble movements of the limbs. The muscles are atonic or markedly hypotonic. The Moro response is usually absent or very weak. Prominent symp-

toms are exhibited by the bulbar muscles in the form of feeble or voiceless crying, inability to suck, difficulty in swallowing and breathing, and an expressionless face.

The extraocular muscles are rarely affected Ptosis is also uncommon This is in contrast to the symptoms in juvenile and adult patients in whom involvement of the extraocular muscles is most common.

Aspiration of formula and mucus may occur if the infant is unable to swallow, which may further embarrass an already depressed respiration In severe cases, if undiagnosed and untreated, death usually occurs in respiratory failure.

Natural Course

Neonatal myasthenia gravis is an illness of short duration Its natural course usually lasts from a few hours to seven weeks Recovery is complete Cases have been followed as long as five years and have shown no signs of recurrence The transitory nature of this syndrome suggests the presence of a substance passing from the mother to the infant which is slowly excreted or destroyed during the neonatal period There is no proof of this theory, however. One of our cases of juvenile myasthenia born of a myasthenic mother may well have been a most unusual form of the transient type which has persisted This will be more fully discussed in the section on juvenile myasthenia gravis

Diagnosis

The diagnosis of transient neonatal myasthenia gravis is not difficult to establish if it is borne in mind that a myasthenic mother may give birth to an infant affected by the same syndrome Once this condition has been noted in the mother, the pregnancy should be particularly suspect and followed closely at term A newborn infant of a myasthenic mother whose previous pregnancy resulted in a neonatal death of undetermined etiology should be carefully observed for signs of this syndrome It is the combined duty of the physician who treats the mother for her myasthenic disorder, the obstetrician who delivers her, and the pediatrician who cares for the infant to watch for the possible development of signs and symptoms of myasthenia in such newborns.

Whenever an infant born of a myasthenic mother develops bulbar symptoms, neonatal myasthenia gravis should be suspected rather than intracranial birth injury These two conditions can be differentiated by an injection of 0 1 ml of Tensilon[86, 90] either intramuscularly or subcutaneously (Tensilon in this dosage has been administered without any hazard) If the baby responds to the test by almost immediate relief of symptoms, the diagnosis is established. Prior to the use of the Tensilon test, the diag-

nosis was made by subcutaneous or oral Prostigmin, as reported in 21 of the cases.

Treatment

Neonatal myasthenia gravis is comparatively uncommon and individual experience is limited in the treatment of such patients. In the milder forms of this disorder, the patient may recover completely without specific therapy with anticholinesterase drugs. However, this may be hazardous as, in the five patients reported who were not treated, two deaths resulted, one on the third and the other on the fourth day after birth. Eighteen patients were given Prostigmin and six Mestinon: one treated with Prostigmin died on the seventh day from sudden cyanosis and respiratory failure (cholinergic death?).[87]

Anticholinesterase drugs should be given whenever it is indicated by the presenting symptoms, such as difficulty in breathing, swallowing, or inability to suck. In the milder forms without bulbar symptoms, medication can be withheld. Nevertheless, the infant should be closely watched for the development of the aforementioned signs and therapy with anticholinesterase drugs should be instituted as soon as they are noted.

The dosage of Prostigmin used in these patients varied from 0.05 mg to 1.0 mg of the injectable preparation and from 1.0 mg. to 5.0 mg by mouth with each feeding. This range indicates that the adequate dose of anticholinesterase drug differs in each individual case. In the majority of cases a successful result has been attained with 1.0 to 2.0 mg oral Prostigmin. Exceeding care should be taken in the adjustment of the proper dosage. The use of Mestinon[91,92] is preferred because it is less toxic, having fewer muscarinic side-reactions. The pharmacy can make a syrup of Mestinon so that one drop equals 1 mg. of Mestinon bromide and 5 drops (5 mg.) can be added to the feeding. In the injectable form 0.1 ml. to 0.2 ml (0.2 to 0.4 mg.) Mestinon is used. Injectable Mestinon and Prostigmin are thirty times as effective as the oral type. If a small dose of 5 to 10 mg of Mestinon or 1 to 2 mg. of Prostigmin every four hours with each feeding can bring about satisfactory sucking, swallowing and adequate respiration, then this dosage should be maintained without further increase for the purpose of achieving loud crying or better strength in limb movements. The latter conditions do not threaten the life of the patient. Moreover, since the condition is of short duration, there is no need to be overvigorous in treatment. All six of our neonatal cases are currently living in complete remission.

After the first week of treatment with anticholinesterase drugs, an attempt at gradual withdrawal should be made. If this fails, the original dosage should be reinstituted and the procedure should be tried again

...weakness ... differentiate myasthenic and
If undesirable ...
tion of saliva
should be redu...
amounts of atropine, but atropine should not be used routinely [93] Supplementary therapy with incubator, oxygen, repeated suction of the oronasapharyngeal cavity and antibiotics should be used as indicated Careful, watchful, excellent nursing care is essential

Juvenile Myasthenia Gravis

Myasthenia gravis in children has been diagnosed more frequently in the past twenty years Over 190 cases have been reported in the literature In 1956, Teng and Osserman [84] reported 19 cases which are briefly summarized in Table 23

Eight additional cases have been seen at The Mount Sinai Hospital since this report

Age and Sex

Eighteen patients are female and nine are male The age varied from ten months to seventeen years when first seen

Onset

In this group, myasthenic symptoms were first noted at birth in seven patients, 48 hours after birth in one patient, one to one and one-half years old in six patients, two years in two patients, seven years in two patients, ten years in one, twelve to seventeen years in eight patients Eight could be defined as the so-called "congenital" type and nineteen as the "acquired" type [93]

Family History

Myasthenia gravis is said not to be an hereditary disorder. This is fairly well borne-out in studies of the family history in the adult form In our entire adult group we have only two incidences of sibling myasthenia, a brother and sister and two sisters *

In the juvenile form of myasthenia the frequency of sibling incidence is much greater, in fact, nine of 27 patients had some form of family history, including brothers, sisters, and first cousins Only one mother o...

* These sisters were recorded in 1913 as having the onset during adolescence [21]

Case #	Sex	Age	Onset	Chief Symptoms	Mestinon Bromide Therapy	Results Remarks
1	M	13 yrs	1-1½ yrs.	Bilateral ptosis and ophthalmoplegia, weakness in legs and arms.	120 mg. t i d.	Weakness in limbs improved. Ophthalmoplegia slightly improved.
2	F	9 yrs	Birth	Bilateral ptosis and opththalmoplegia, weakness in limbs, difficulty in swallowing	120 mg q3h, daytime only	Partial improvement of ocular symptoms Others markedly improved.
3	M	17 yrs	Birth	Bilateral ptosis and ophthalmoplegia, weakness in limbs	120 mg. q4h, daytime only	Partial improvement of ocular symptoms Others markedly improved
4	F	9 yrs.	7 yrs.	Bilateral ptosis, weakness in limbs and neck, slurred speech	60 mg. Mestinon bromide and 15 mg. Prostigmin q3h, daytime only.	Symptom-free except for ophthalmoplegia.
5	F	26 months	1½ yrs.	Bilateral ptosis, ophthalmoplegia, difficulty breathing and swallowing, slurred speech, weakness in limbs and neck.	30 to 90 mg q i d	Symptom-free.
6	F	2 yrs.	1½ yrs.	Bilateral ptosis, ophthalmoplegia, head to right, difficulty in swallowing, frequent falls, slurred speech, weakness in limbs	30 to 40 mg. q4h q i d	Died from bronchopneumonia
7	M	10 months	Birth	Bilateral ptosis, ophthalmoplegia, weakness in limbs, weak cry.	35 drops syrup† each feeding	Symptom-free
8	F	3 yrs.	Birth	Bilateral ptosis, ophthalmoplegia, weakness in limbs, sleepy look	60 mg t i d	Symptom-free.
9	M	38 weeks	48 hrs after birth	Bilateral ptosis, general weakness, poor sucking.	10 mg q4h, daytime only	Symptom-free
10	F	12 yrs.	12 yrs	Bilateral ptosis, ophthalmoplegia, weakness in limbs	50 to 90 mg q5h, daytime only	Remission

Case #	Sex	Age	Onset	Chief Symptoms	Mestinon Bromide Therapy	Results Remarks
11	M	8 yrs	2 yrs	General weakness, sleepy, weakness in limbs	30 mg q i d	Symptom-free
12	F	13 yrs	7 yrs.	Bilateral ptosis, ophthalmoplegia, weakness in limbs, slurred speech	120 mg t i d	Ptosis improved, ophthalmoplegia slightly improved Marked improvement in limb strength
13	F	17 yrs	16 yrs	Crisis, difficulty in swallowing and breathing, marked general weakness, ophthalmoplegia, later became disassociated	17 5 mg i m q2½h 240 mg (oral) b i d to t i d	Improved after thymectomy
14	F	14 yrs	14 yrs	Diplopia only	90 to 120 mg t i d	Remission.
15	M	6 yrs	1 yr	Bilateral ptosis ophthalmoplegia, inability to walk, difficulty in swallowing, chewing, speech	360 mg q3h Changed to 60 mg Mestinon with 10 mg Mytelase q4h	Improved
16	F	2¼ yrs	2 yrs	Bilateral ptosis weakness in lateral movement O S , generalized weakness	120 mg q4h (Tried on Mytelase 15 mg preferred Mestinon)	Residual ptosis
17	F	2 yrs	1 yr	O D Ptosis, generalized ptosis	30 mg t i d	Symptom-free
18	M	4¼ yrs	Birth	Bilateral ptosis, trunk and extremity weakness slurred speech slow learning frequent choking Tracheotomy at 3 months	30 mg t i d	Improved
19	F	5½ yrs	10½ months	Bilateral ptosis difficulty in swallowing trunk and extremity weakness some respiratory weakness	60 mg t i d	Symptom-free

* Reprinted, by permission, from Teng P and Osserman K E J Mt Sinai Hosp 23 711, 1956
† Syrup Mestinon—Pharmacy prepared syrup so that 1 drop equals 1 mg

one juvenile patient is myasthenic. This patient had a history of difficulty in sucking and swallowing and of choking on feeding at birth. The mother stated that all symptoms disappeared in "several weeks" without specific medication. Later at the age of two to three years, frequent stumblings and general muscular weakness were noted. The latter symptom became more marked at the age of nine years. Judging from the history, this patient might have had the transient neonatal type which disappeared in his early infancy. Two years later the juvenile type developed.



Fig 57. A rare case in which both mother and child have myasthenia

All the other cases were born of nonmyasthenic mothers. This is in contrast to transient neonatal myasthenia which invariably occurs in infants born to myasthenia mothers.

The review of the literature contained in Table 24 shows a similar high familial incidence.[7,12,21,24,25] In spite of this frequency, a genetic basis in myasthenia gravis is difficult to accept.

Symptomatology

The symptoms and signs observed in children differ from those in adult patients. The distinguishing characteristic in children is the generalized bilateral and symmetric distribution of weakness, involving the eyes, face,

neck, body and limbs In adults, weakness is frequently asymmetric, in volving one part of the body more than another.

Ptosis Bilateral symmetric ptosis was observed in 22 and unilateral in 3 of 27 patients In adult patients the incidence of ptosis is 78 per cent, 24 per cent being unilateral and 54 per cent bilateral.

Ophthalmoplegia A bilateral symmetric ophthalmoplegia has been noted in 15 of 27 patients Teng and Osserman's analysis of the cases of ophthalmoplegia reported in the literature appears in Table 24

Eight patients showed a complete form, with the eyes at a centering position The other seven showed an incomplete form or symmetrically limited ocular movements, i e, both eyes retained some degree of lateral and/or vertical movement. All these movements were in conjugation In adult patients, 70 per cent had extraocular muscle involvement and in all except four cases the involvement was asymmetric and disconjugated All these adults had diplopia This difference between children and adults has been previously noted 25



Fig 58 Juvenile myasthenia showing ophthalmoplegia

Eighteen of the thoroughly reported cases had ophthalmoplegia. Ten of these 18 patients had a complete bilateral type and the others had a symmetric, incomplete form Invariably all these patients had bilateral

Table 24 *Bilateral Ophthalmoplegia.**

Author	*First Examined*	*Sex*	*Onset*	*Relationship*	*Description*
Hart, 1927	17 yrs	F	9 years	Sisters	Complete ophthalmoplegia.
	19 yrs.	F	14 yrs		Complete ophthalmoplegia.
Rothhart, 1937	9 yrs.	M	6 weeks	Brothers	Partial ophthalmoplegia
	15 yrs.	M	3 yrs.		Partial ophthalmoplegia.
Riley & Frocht, 1943	26 yrs	F	11 yrs.	Sisters	Complete ophthalmoplegia
	19 yrs	F	14 yrs		Complete ophthalmoplegia.
Heinzen, 1955	13 yrs	M	Birth		Complete ophthalmoplegia.
Schlif, 1955	22 yrs.	F	Birth		Partial ophthalmoplegia
Bowman, 1948	3 1/12 yrs.	M	Birth	Cousins	Practical absence of ocular movement.
	4 6/12 yrs.	M	3 1/12 yrs.		Practical absence of ocular movement.
	8 7/12 yrs.	F	4 yrs.		Marked diminished ocular movement in all directions
Levin, 1949	4 yrs.	F	Birth	Sisters	Partial ophthalmoplegia.
	1 yr.	F	Birth		Partial ophthalmoplegia.
Walsh, 1949	3 yrs.	F			Complete ophthalmoplegia
	5 yrs.	M			Complete ophthalmoplegia
Macrae, 1954	3 yrs.	M	Birth		Virtually no ocular movements.
Wyllie et al 1951	9 yrs.	F	8 yrs.		Restricted ocular movements
Mackay, 1951	9 yrs	F	Birth	A binovular twin, normal	Complete ophthalmoplegia

Author	First Examined	Sex	Onset	Relationship	Description
Teng and Osserman, 1958	13 yrs.	F	7 yrs	A first cousin, 23 yrs old, has had myasthenia gravis since childhood	Complete ophthalmoplegia.
	13 yrs	M	1-1½ yrs.	First cousin to the next 2 patients.	Complete ophthalmoplegia
	9 yrs	F	Birth	A normal binovular twin	Complete ophthalmoplegia.
	17 yrs	M	Birth	Brother and sister.	Almost complete ophthalmoplegia.
	3 yrs	F	Birth	Sister	Partial ophthalmoplegia
	10 months	M	Birth	Brother	Partial ophthalmoplegia
	2 yrs	F	1¼ yr		Almost complete ophthalmoplegia.
	17 yrs	F	Acute onset at 16 yrs		Complete ophthalmoplegia
	2 yrs	F	1½ yrs		Complete ophthalmoplegia.
	12 yrs	F	12 yrs		Partial ophthalmoplegia
	6 yrs	M	Infancy		In complete ophthalmoplegia

• Reprinted, by permission, from Teng, P., and Osserman, K. E. J. Mt. Sinai Hosp. 23: 711, 1956.

symmetric ptosis The two sisters mentioned above retained their ophthalmoplegia and ptosis into adult life.

Bilateral complete ophthalmoplegia is one of the prominent features in adult patients in crises and was observed in eight of our patients who were in such a state

Other types of abnormal eye movement in symmetric fashion, such as convergence strabismus, difficulty in convergence and disconjugation of eye movement of the adult type, have also been noted in children

Diplopia. Diplopia is uncommon in children. Five of 27 patients had occasional transient diplopia.

Weakness in Facial Muscles. Involvement of the facial muscles in children is frequent and is symmetric. In 24 of 27 patients facial weakness was noted before treatment. The patients showed the expressionless face frequently described in the literature as "myasthenia face", long-drawn, sad-looking, with lack of animation. In the adult the incidence of this symptom is 36 per cent.

Difficulty in Swallowing, Speech and Respiration. Difficulty in swallowing was observed in 16 of these 27 patients Four children also had respiratory distress Slurred speech or weak crying was noted in seven These symptoms were more frequently observed in children below the age of two years The presenting symptoms in this age group were similar to those displayed by the neonatal group, as described above.

Weakness in Skeletal Muscles The involvement of the skeletal muscles in children is generalized and symmetric, this has been observed in all 27 cases Younger children manifested delayed or weak walking, frequent stumblings, awkward gait or limpy limbs with muscular hypotonia Older children tired easily, had sagging shoulders, a sleepy appearance and were incapable of sustained activity.

Diagnosis

If the physician is aware of the myasthenic syndrome, the diagnosis of juvenile myasthenia gravis is not difficult to establish In children with myasthenia gravis, the bulbar symptoms may simulate poliomyelitis. The differential diagnosis can be made by the subcutaneous or intramuscular injection of 0 2 ml. of Tensilon, which relieves the presenting symptoms only in myasthenia gravis In the newborn, if there is a family history of the disease, myasthenia gravis should be suspected The diagnostic dose of Tensilon for the newborn is 0.1 ml A positive Tensilon test should be followed by a therapeutic trial with anticholinesterase drugs such as Mestinon or Prostigmin.

Treatment

Of 27 patients, five are now in remission and require no medication. Sixteen are taking Mestinon, four take Prostigmin and two take Mytelase. The dosage was varied in each individual case according to the age of the patient and the severity of the condition. In infants and young children a trial dose of 10 mg of Mestinon orally was given. If no significant signs of improvement were observed, the dose was increased by 5 mg increments until a satisfactory result was obtained. The use of a syrup in which 1 teaspoon equals 1 Mestinon (60 mg) tablet yielding 1 mg per drop is very helpful in estimating the amount needed. In older children, one-quarter scored tablets were used. The initial dose was generally one-half tablet, which was increased by one-quarter tablet increments until satisfactory results were attained. The Tensilon test was frequently used in the management of these cases.

Of the 27 cases, two were thymectomized and 25 were treated medically. Seven achieved complete remission, of which five remain in remission. Six were clinically improved, with marked reduction in medication possible. Eight were clinically improved but no reduction in medication was possible. Four remained basically unchanged even though receiving medication. Two experienced exacerbations and three died.

The question of thymectomy in juvenile myasthenia gravis is thoroughly discussed in the Chapter on Surgical Treatment, however, Keynes' report[59] of 15 type A and B remissions in 21 children of both sexes who underwent thymectomy should be emphasized here. In our series 15 of 25 patients achieved the A or B classification of Keynes under medical treatment, a remission rate of 55 per cent. When the C classification is added, the rate is raised to 81 per cent. Keynes' surgical remission rate is 71 per cent. Until more cases are operated upon and evaluated, however, this procedure in children must be undertaken with great caution.

Prognosis

In juvenile myasthenia gravis the improvement under medical therapy is almost identical to that observable in the localized (Group I) adult form. The mortality rate in adult patients varies from 13 to 23 per cent.[24] Our wn incidence in adult patients is 15 per cent, in the juvenile form 10.6 er cent.

This disorder in children responds well to treatment. Crisis occurs very requently as compared to adults. The literature reveals few spontaous remissions, however, five of our patients are in complete remission. enile patients have to be treated continuously with an adequate unt of anticholinesterase drug.

Systemic or upper respiratory infection almost always aggravates t symptoms and should be vigorously treated with antibiotics. At times, spite of increased anticholinesterase medication, symptoms are not sat factorily controlled during the course of infection.

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CHAPTER XVIII

Associated Diseases

IN THE GROUP of 325 patients seen at The Mount Sinai Hospital, the ollowing associated diseases were present

Malignancy (other than in the thymus)		8
Rheumatic fever or chorea		4
Coronary thrombosis		4
Angina pectoris		2
Benign hypertension		17
Chronic glomerular nephritis		1
Nephrolithiasis		3
Requiring surgery		2
Syphilis		1
Anterior poliomyelitis		2
Infectious mononucleosis		1
Brucellosis		2
Tuberculosis		3
Infectious hepatitis		2
Gastric ulcer		4
Mucous colitis		1
Glaucoma		3
Epilepsy		2
Arthritis		11
Rheumatoid	4	
Bronchial asthma		6
Diabetes mellitus		8
Hyperthyroidism		11
Functional hypoglycemia		1
Alcoholism		1
Depression		14
Electric shock therapy	8	
Insulin shock therapy	1	

As can be seen from this listing, with the exception of hyperthyroidism and psychiatric depression there is no significant occurrence of any other disease with myasthenia gravis. The frequency of occurrence of these conditions is not out of proportion to that in the general population.

The concomitant illness, such as diabetes, epilepsy, malignancy, coroary thrombosis, is treated in the routine manner, with the following ceptions:

Infection Infections are treated routinely with antibiotics as indicated.

In those patients in whom upper respiratory infection causes marked exacerbation of myasthenia, preventive therapy in the form of a daily dose of an antibiotic has been instituted, with good results.

Some investigators have stated that aspirin causes an increase in myasthenic symptomatology, but, to date, we have used it with no difficulty. It would seem probable that the underlying condition for which the patient takes the aspirin is the cause of the increased symptomatology rather than the aspirin

Quinine and curare have both been found to aggravate myasthenic symptoms severely and as such have been advocated as diagnostic tests for this condition These drugs are never prescribed for the patient with myasthenia gravis Quinine is found in some anticold tablets or is used as an antimalarial agent, but other drugs must be substituted in the myasthenic patient.

Drugs such as codeine and Demerol may be prescribed as indicated, either alone or in combination with aspirin or cough syrup.

Glaucoma Use of anticholinesterase drugs in the treatment of myasthenia gravis is also helpful to glaucoma when it occurs Atropine, which is used as an antidote to overdosage with anticholinesterase drugs, must be avoided since it is contraindicated in glaucoma

Gastric Ulcer and Colitis Mytelase, or possibly Mestinon, is the best drug to use in the treatment of patients with concomitant gastric ulcer or colitis, since these drugs have much fewer muscarinic side-effects on the gastrointestinal tract than does Prostigmin.

Rheumatoid Arthritis and Asthma Patients with rheumatoid arthritis or asthma should be treated in a conservative manner, avoiding the use of the corticosteroids or ACTH If these drugs are essential for the patient's health, they may be prescribed if the patient is hospitalized for very close observation and frequent adjustment of the anticholinesterase drugs. Increased anticholinesterase medication will be needed to overcome the deleterious effects of the ACTH or the corticosteroids on the myasthenic symptomatology The attempted use of the steroids to induce remission is discussed elsewhere

Cardiac Arrhythmias. In the case of supervening cardiac arrhythmia it is safer to treat the arrhythmia with Pronestyl and/or digitalis rather than quinidine since the latter is a quinine derivative and is contraindicated in myasthenia gravis.

Hyperthyroidism. Hyperthyroidism is fully discussed in the Chapter on Endocrinology Administration of thyroid extract to myasthenic patients, even in the presence of a low basal metabolic rate, does not seem justifiable. In the few cases which tended toward myxedema following therapy

for hyperthyroidism, however, the use of ¼ to ½ gr of thyroid daily improved the myxedema considerably

Hypertension. Hypertension is best treated with mild sedation and the usual antihypertensive drugs

Depression Psychiatric help may be required in the more severe depressions. The physician can help the patient with milder emotional problems by taking the time to listen and encourage him

The introduction of the tranquilizers, particularly those of the meprobamate type such as Miltown and Equanil, has posed a problem concerning their use in myasthenia gravis Since many myasthenics have a tendency to be apprehensive, the use of a tranquilizer in place of barbiturates is very tempting. These drugs have a muscle relaxant activity similar to that of Tolserol and are, therefore, theoretically contraindicated However, they have been used sparingly with no great difficulty, and capsules of chloral hydrate for the milder cases and Thorazine, Sparine or Compazine for the more seriously anxious patients are excellent drugs if used with caution.

A number of our myasthenics have been treated with electroshock therapy because of severe depression In these cases, withholding of the anticholinesterase drug placed the patient in a relaxed state almost similar to that of the curare-treated nonmyasthenic patient

From the listing given, it would seem that the incidence of severe psychiatric problems in myasthenia gravis is greater than that which occurs in the normal population It must be remembered that this is a chronic disorder that may influence the attitude of the patient The incidence of shock therapy in other chronic illnesses has not been fully evaluated so a comparison cannot be made, but the impression is that in Parkinsonism also there is a large percentage of need for this type of therapy In multiple sclerosis and tuberculosis the patient is somewhat protected from the psychological impact of the condition by the euphoria induced by the illness

Surgery Surgery is performed as indicated following the precautions discussed in Chapter XIV, such as the avoidance of curare for anesthesia, morphine and enemas Demerol, and codeine are excellent drugs to relieve pain and are not contraindicated in myasthenia gravis.

The myasthenic patient may develop secondary infection, degenerative disease or malignancy which must be treated. The two important points to remember in treating associated diseases is that certain drugs are contraindicated in myasthenia gravis. curare, quinine, quinidine, and morphine, certain drugs must be used with caution ACTH, corticosteroids, thyroid compounds, and respiratory depressants, sedatives may be used in small doses The second point is that associated diseases such as infec-

tion may alter the patient's need for anticholinesterase medication so that dosages must be watched carefully and adjusted as necessary. As discussed in the Chapter on Management, the Tensilon test is of great value in dealing with this problem.

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CHAPTER XIX

Prognosis

UNTIL THE MID-1930's no specific treatment for myasthenia gravis was available. The mortality figures showed this condition to be truly "gravis" 80 per cent [1] of patients were dead within a year of onset of this disorder, 50 per cent of the remaining patients died in the second year. An ameliorating factor may have been that milder cases went undiagnosed until the Prostigmin test was introduced.[2] In recent years the Tensilon test has been helpful in identifying early cases of myasthenia.[3]

The prognosis for the patient suffering from a myasthenic syndrome now is greatly improved as a result of the knowledge accumulated by the pharmacodynamist in the form of new drug therapies and the clinician's growing comprehension of methods of proper drug administration. Radiotherapy, surgery and psychotherapy also contribute to the better treatment of the patient.

From a clinician's view the following have been the most important factors in improving the prognosis in these patients:

1. Excellent anticholinesterase drugs are available for treatment.
2. It is now recognized that *overdosage* with anticholinesterase drugs can lead to cholinergic reaction. If unheeded, crisis and death may occur.[4] This recognition of overdosage has reduced the mortality figures. A corol-ary is the fact that atropine, an antimuscarinic drug, is most helpful in vercoming cholinergic reaction when it occurs. The drugs PAM and AM can overcome severe nicotinic reactions.[5]
3. The Tensilon test used in management[6] has proven to be most important because of the objective evidence it gives of results of treatment with specific drugs.
4. Radiotherapy[7] and thymectomy[8-10] have been used in some patients to influence the course of myasthenia gravis favorably.
5. The use of mechanical respirators and proper tracheal-bronchial toilet to keep air passages open has been of great value in keeping myasthenia patients alive when in crisis.[11]
6. The clinical classification of myasthenic syndromes and the evaluation key (Chapter IV) have been valuable in determining the prognosis and in selecting proper therapy for the individual patient.

The first two years of the disease are the most important. Most remissions occur during this period and so do most crises and deaths.[12] By the end of two years the type of myasthenia is generally established. In only

31 of 136 cases in whom ocular symptoms alone were present at onset did the condition become sufficiently exacerbated to be classified as the late severe form of myasthenia. The symptoms in one other case spread from another localized form of myasthenia. On the other hand, remissions, although occurring largely in the first two years of the condition, may occur as late as the twenty-fifth year of the illness. Myasthenia crises tend to decrease after the first few years, although cholinergic crisis may occur at any time

TABLE 25 *Remission.*

1. "A": Remission = a patient without symptoms and untreated with drugs for at least three months
2. *77 patients out of 325 (excluding neonatal), or 24%, had a total of 84 remissions*
3. 43 patients remain in remission (excluding neonatal)
4. Average duration 2 8 years Spread. 3 months to 23 years.

Current "A" Remission

Age	*Females*	*Males*
Under 30	13	1
Over 30	17	12
	30	13

5.

Year of Disease	*Number of Remissions*
1	27
2	16
3	3
4	4
5	3
6-10	15
11-15	11
16-20	2
21-25	3
Total	84

Analysis of the sex-age factor shows that in Group I the sexes are equally divided, whereas in Group II the ratio is four females to one male, in Group III two and one-half females to one male, Group IV two females to one male and in Group V three and one-half females to one male. Men usually develop myasthenia later in life and tend to have a localized, milder form than the female. Males who have an acute fulminating onset (Group III) are more recalcitrant to treatment than females Because of their sex they are not candidates for thymectomy, unless they have a concomitant thymoma which warrants removal regardless of the myasthenia.

Table 26, based on The Mount Sinai Hospital series, gives the over-all death rate, the year of occurrence of death after onset and the number of patients surviving up to 47 years. This table indicates that myasthenia does not necessarily cause death and that many patients are alive today twenty or more years after the onset of symptoms. Thirty-six of the 57 deaths occurred within the first two years of the disease, most of these deaths were in patients in Groups III, IV or V.

TABLE 26

Year	*Number of Cases*	*Deaths* *Myasthenic*	*Nonmyasthenic*
0	57	19	1
1	29	10	1
2	33	4	1
3	35	4	0
4	17	3	1
5	17	1	1
6	21	2	0
7	8	2	0
8	12	0	1
9	9	1	0
10	6	1	0
11	9	0	0
12	6	0	0
13	7	0	0
14	7	0	0
15	4	0	0
16	6	0	0
17	4	0	1
18	6	0	2
19	4	1	0
20	5	0	0
21	3	0	0
22	6	0	0
23	3	0	0
24	2	0	0
25	–	0	0
26	6	0	0
33	1	0	0
35	1	0	0
47	1	0	0
Totals	325	48=15%	9

Certain conclusions regarding prognosis can be established

1 The mortality rate in myasthenia gravis has been markedly decreased, to the point where it is less than one-fourth the rate before the introduction of anticholinesterase drugs.

2. The patient's life expectancy will be relatively unaffected by the disorder if he survives the first two years.

3 Remission rates, although highest in the first two years may occur as late as the third decade after the onset of symptoms.

4. The appearance of thymoma influences the course of myasthenia unfavorably.

Clinical classification is most helpful in selecting proper therapy for the patient Within a few months of the onset of symptoms, it is usually possible to classify the patient properly. Relatively good results can be expected with drug therapy in the pediatric, localized and generalized forms of myasthenia If the patient has an acute fulminating onset or later in the course of the illness develops a late severe or a muscle atrophy type, one must treat with drugs with the realization that the results may not be satisfactory. The physician must be prepared to use other modalities, such as radiotherapy, or thymectomy in the young female, in an attempt to influence the course of the disorder favorably.[11]

The question or early thymectomy in milder cases is as yet not completely resolved. The centers which are performing this operation are certainly most enthusiastic about their results, but at the present time, one should probably take a more conservative stand and await more convincing reports before resorting to routine thymectomy in the *mild* case

In a Symposium on Myasthenia Gravis, Viets[13] stated that the basic problems of myasthenia are junctional transmission, the relationship of the thymus to myasthenia and the problem of medical care. He remarked that the basic cause of the disorder still eludes us, as does the reason for its onset at various ages, the causes of relapse and remission, the transmission of symptoms to the child by the mother with the illness, the reasons for its variable location in particular muscle groups and the problem of atypical cases which show drug resistance. These challenges set the pattern for future research.

Research is constantly in progress. The answer may lie in biochemistry or biophysics. What role the endocrines play is still not clear. The humoral elements have been subjected to study only recently.

For the physician who treats the myasthenic patient there can be great gratification. When in the course of differential diagnosis, patients are found to have other conditions as the cause of muscular weakness, particularly the neurologic entities such as multiple sclerosis and amyotrophic lateral sclerosis or disorders of the muscles such as muscular dystrophy, the physician at present can impart very little hope to the patient and his family On the other hand, if myasthenia gravis is established, one can almost call this a hopeful diagnosis, and the patient can be told that although he has a serious chronic disorder, he can be helped. Excellent

drugs are now available for treatment A clinical test, the Tensilon test, can be used to guide management of his drug dosage An operation, thymectomy, may favorably influence the condition Ancillary treatment in the form of radiotherapy may be utilized if necessary The patient can be told, too, that myasthenia is not hereditary and that, in general, he can expect to live out the normal number of years Since there is no pathologic defect in myasthenia gravis, if a cure should be discovered, the patient could be restored to normality. Finally, the occurrence of spontaneous remission and the possibility of inducing remission with the various means already mentioned, all of these things make it feasible to term myasthenia this a disorder with hope

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